Medical Policy

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***Current Policy Effective Date: 9/1/24**
(See policy history boxes for previous effective dates)

Title: Intravitreal and Punctum Corticosteroid Implants

Description/Background

An intravitreal implant is a drug delivery system, injected or surgically implanted in the vitreous of the eye, for sustained release of a pharmacologic agent to the posterior and intermediate segments of the eye. Four intravitreal corticosteroid implants, ie, fluocinolone acetonide 0.59 mg (Retisert), fluocinolone acetonide 0.19 mg (Iluvien), fluocinolone acetonide 0.18 mg (Yutiq) and dexamethasone 0.7 mg (Ozurdex) are reviewed herein. Fluocinolone acetonide implants are non-erodible and deliver drug up to 30 to 36 months while dexamethasone implants are bioerodible and last up to 6 months.

A punctum implant is a drug delivery device that is inserted through the lower lacrimal punctum into the canaliculus, for sustained release of a pharmacologic agent to the ocular surface. Dexamethasone ophthalmic insert 0.4 mg (Dextenza) is the first corticosteroid intracanalicular insert and is reviewed herein.

EYE CONDITIONS

Uveitis

Uveitis encompasses a variety of conditions, of infectious or non-infectious etiologies, that are characterized by inflammation of any part of the uveal tract of the eye (iris, ciliary body, choroid). Infectious etiologies include syphilis, toxoplasmosis, cytomegalovirus retinitis, and candidiasis. Non-infectious etiologies include sarcoidosis, Behcet's disease, and "white dot" syndromes such as multifocal choroiditis or "birdshot" chorioretinopathy. Uveitis may also be idiopathic, have a sudden or insidious onset, a duration that is limited (less than 3 months) or persistent, and a course that may be acute, recurrent, or chronic.

The classification scheme recommended by the Uveitis Study Group and the Standardization of Uveitis Nomenclature (SUN) Working Group is based on anatomic location. Patients with anterior uveitis typically develop symptoms such as light sensitivity, pain, tearing, and redness of the sclera. In posterior uveitis, which comprises approximately 5% to 38% of all uveitis cases in the U.S., the primary site of inflammation is the choroid or retina (or both). Patients with intermediate or posterior uveitis typically experience minimal pain, decreased visual acuity, and the presence of floaters (bits of vitreous debris or cells that cast shadows on the retina). Chronic inflammation associated with posterior segment uveitis can lead to cataracts and glaucoma and to structural damage to the eye, resulting in severe and permanent vision loss.

Treatment

The primary goal of therapy for uveitis is to preserve vision. Non-infectious uveitis typically responds well to corticosteroid treatment. Immunosuppressive therapy (e.g., anti-metabolites, alkylating agents, T-cell inhibitors, and tumor necrosis factor [TNF]-inhibitors) may also be utilized to control severe uveitis. Immunosuppressive therapy is typically reserved for patients who require chronic high-dose systemic steroids to control their disease. While effective, immunosuppressants may have serious and potentially life-threatening adverse effects, including renal and hepatic failure and bone marrow suppression.

Macular Edema After Retinal Vein Occlusion

Retinal vein occlusions are classified by whether the central retinal vein or one of its branches is obstructed. Central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) differ in pathophysiology, clinical course, and therapy. Central retinal vein occlusions are categorized as ischemic or nonischemic. Ischemic CRVOs are referred to as severe, complete, or total vein obstruction and account for 20-25% of all CRVOs. Macular edema and permanent macular dysfunction occur in virtually all patients with ischemic CRVO, and in many patients with nonischemic CRVO. BRVO is a common retinal vascular disorder in adults between 60 and 70 years of age and occurs approximately 3 times more commonly than CRVOs.

Treatment

Intravitreal injections of triamcinolone are used to treat macular edema associated with CRVO, with a modest beneficial effect on visual acuity. The treatment effect lasts about six months, and repeat injections may be necessary. Cataracts are a common side effect, and steroid-related pressure elevation occurs in about one third of patients, with 1% requiring filtration surgery.

Macular photocoagulation with grid laser improves vision in BRVO but is not recommended for CRVO. Although intravitreal injections of triamcinolone have also been used for BRVO, the serious adverse effects have stimulated the evaluation of new treatments, including intravitreal steroid implants or the intravitreal injection of anti-vascular endothelial growth factor.

Diabetic Macular Edema

Diabetic retinopathy is a common microvascular complication of diabetes and a leading cause of blindness in adults. The two most serious complications for vision are diabetic macular edema and proliferative diabetic retinopathy. At its earliest stage (nonproliferative retinopathy), microaneurysms occur. As the disease progresses, blood vessels that provide nourishment to the retina are blocked, triggering the growth of new and fragile blood vessels (proliferative retinopathy). Severe vision loss with proliferative retinopathy arises from leakage of blood into the vitreous Diabetic macular edema is characterized by swelling of the macula due to gradual leakage of fluids from blood vessels and breakdown of the blood-retinal barrier. Moderate vision

loss can arise from the fluid accumulating in the center of the macula (macular edema) during the proliferative or nonproliferative stages of the disease. Although proliferative disease is the main blinding complication of diabetic retinopathy, macular edema is more frequent and is the leading cause of moderate vision loss in people with diabetes.

Treatment

Tight glycemic and blood pressure control is the first line of treatment to control diabetic retinopathy, followed by laser photocoagulation for patients whose retinopathy is approaching the high-risk stage. Although laser photocoagulation is effective at slowing the progression of retinopathy and reducing visual loss, it does not restore lost vision. Alternatives to intravitreal implants include intravitreal injection of triamcinolone acetonide, which is used as an off-label adjunctive therapy for diabetic macular edema. Angiostatic agents such as injectable vascular endothelial growth factor inhibitors, which block stages in the pathway leading to new blood vessel formation (angiogenesis), have demonstrated efficacy in DME.

Age-Related Macular Degeneration

Age-related macular degeneration is a degenerative disease of retina that results in loss of central vision with increasing age. Two different forms of degeneration, known as dry and wet, may be observed. The dry form (also known atrophic or areolar) is more common and is often a precursor to the wet form (also known as exudative neovascular or disciform). The wet form is more devastating and characterized by serous or hemorrhagic detachment of the retinal pigment epithelium and development of choroidal neovascularization (CNV), which greatly increases the risk of developing severe irreversible loss of vision. CNV is categorized as classic or occult.

Treatment

Effective specific therapies for exudative or wet age related macular degeneration are an intravitreous injection of a vascular endothelial growth factor inhibitor, possibly thermal laser photocoagulation (in selected patients), and photodynamic therapy.

INTRAVITREAL AND PUNCTUM IMPLANTS

Intravitreal and punctum implants deliver a continuous concentration of drug to the eye over a prolonged period. The goal of therapy is to reduce the inflammation in the eye while minimizing the adverse effects of the therapeutic regimen.

Selection of the route of corticosteroid administration (topical, systemic, periocular, or intraocular injection) is based on the cause, location, and severity of the disease. Each therapeutic approach has its own drawbacks. For example, topical corticosteroids require frequent (e.g., hourly) administration and may not adequately penetrate the posterior segment of the eye due to their poor ability to penetrate ocular tissues. Systemically administered drugs penetrate poorly into the eye because of the blood-retinal barrier, and high dose or long-term treatments may be necessary. Long-term systemic therapies can be associated with substantial adverse effects such as hypertension and osteoporosis, while repeated (every 4-6 weeks) intraocular corticosteroid injections may result in pain, intraocular infection, globe perforation, fibrosis of the extraocular muscles, reactions to the delivery vehicle, increased intraocular pressure, and cataract development.

Corticosteroid implants are biodegradable or non-biodegradable. Non-biodegradable systems are thought to be preferable for treating chronic, long-term disease, while biodegradable products may be preferred for conditions that require short-term therapy. Although the

continuous local release of steroid with an implant may reduce or eliminate the need for intravitreal injections and/or long-term systemic therapy, surgical implantation of the device carries its own risks, and the device could increase ocular toxicity due to increased corticosteroid concentrations in the eye over a longer duration. With any route of administration, cataracts are a frequent complication of long-term corticosteroid therapy.

Intraocular corticosteroid implants being evaluated include the following:

- Retisert® (non-biodegradable fluocinolone acetonide intravitreal implant; Bausch & Lomb) is a sterile implant that consists of a tablet containing fluocinolone acetonide 0.59 mg, a synthetic corticosteroid that is less soluble in aqueous solution than dexamethasone. The tablet is encased in a silicone elastomer cup with a release orifice and membrane; the entire elastomer cup assembly is attached to a suture tab. Following implantation (via pars plana incision and suturing) in the vitreous, the implant releases the active drug at a rate of 0.3–0.4 mcg/day over a period of approximately 2.5 years.
- Iluvien™ (non-biodegradable injectable intravitreal implant with fluocinolone acetonide; Alimera Sciences, Inc.) is a rod-shaped device made of polyimide and polyvinyl alcohol. It is small enough to be placed using an inserter with a 25-gauge needle and is expected to provide sustained delivery of fluocinolone acetonide for up to 3 years.
- Ozurdex® (previously known as Posurdex® (biodegradable dexamethasone intravitreal implant; Allergan) is composed of a biodegradable copolymer of lactic acid and glycolic acid with micronized dexamethasone. This implant is placed into the vitreous cavity through the pars plana using a customized, single-use, 22-gauge applicator. The implant provides intravitreal dexamethasone for up to 6 months. The mean number of Ozurdex injections reported in the literature is 4.2 injections per year, and more than 6 consecutive injections have been reported.(1,2)
- Dextenza (biodegradable dexamethasone intracanalicular insert; Ocular Therapeutix) is a rod-shaped hydrogel device that is designed to deliver a sustained and tapered release of 0.4 mg of dexamethasone over four weeks. Following ophthalmic surgery, it is inserted through the inferior punctum into the canaliculus of the operative eye. To allow for visualization and retention monitoring, the hydrogel device is conjugated with fluorescein. No removal is required as the device is designed to resorb and exit the nasolacrimal system independently.
- Yutiq (nonbiodegradable fluocinolone acetonide intravitreal implant; EyePoint Pharmaceuticals U.S., Inc.) is a sterile 3.3 mm-long implant consisting of fluocinolone acetonide 0.18 mg that is preloaded into a single-dose applicator and injected directly into the vitreous. It is designed to provide a sustained release of fluocinolone acetonide at an initial rate of 0.25 mcg/day within over a 36-month period.

Regulatory Status

In 2009, Ozurdex (dexamethasone 0.7 mg intravitreal implant; Allergan) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of macular edema following branch retinal vein occlusion or central retinal vein occlusion. Subsequently, in 2010, the indication was expanded to include treatment of noninfectious uveitis affecting the posterior segment of the eye. In 2014, the indications were again expanded to include treatment of diabetic macular edema.

In 2014, Iluvien (fluocinolone acetonide 0.19 mg intravitreal implant; Alimera Sciences) was approved by FDA for the treatment of diabetic macular edema in patients previously treated with a course of corticosteroids and without a clinically significant rise in intraocular pressure.

In 2004, Retisert (fluocinolone acetonide 0.59 mg intravitreal implant; Bausch & Lomb) was approved by FDA for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye.

In 2018, Yutiq (fluocinolone acetonide 0.18 mg intravitreal implant; EyePoint Pharmaceuticals Inc) was approved by the FDA for treatment of chronic noninfectious uveitis affecting the posterior segment of the eye).

In 2018, Dextenza (dexamethasone 0.4 mg intracanalicular implant; Ocular Therapeutix) was approved by the FDA for the treatment of ocular pain following ophthalmic surgery and in 2019 the FDA extended the approval for inflammation. In October 2021, the indication was expanded to include treatment of ocular itching associated with allergic conjunctivitis.

Medical Policy Statement

The safety and effectiveness of punctum dexamethasone inserts and dexamethasone intravitreal and fluocinolone acetonide intravitreal implants have been established. They may be considered a useful therapeutic option when indicated.

All other uses of intravitreal implant(s) are considered experimental/ investigational.

Inclusionary and Exclusionary Guidelines

Inclusions:

- Fluocinolone acetonide intravitreal implant 0.59 mg (Retisert®) for the treatment of:
  - Chronic non-infectious intermediate, posterior uveitis or panuveitis[a].

- Fluocinolone acetonide intravitreal implant 0.18 mg (Yutiq) for the treatment of:
  - Chronic non-infectious uveitis affecting the posterior segment of the eye[a].

- Fluocinolone acetonide intravitreal implant 0.19 mg (Iluvien™) for the treatment of:
  - Diabetic macular edema in patients who have been previously treated with a course of corticosteroids **AND**
  - Did not have a clinically significant rise in intraocular pressure

- Dexamethasone intravitreal implant 0.7 mg (Ozurdex®) for the treatment of any of the following:

- Non-infectious ocular inflammation, or uveitis, affecting the intermediate or posterior segment of the eye[a]
- Macular edema following branch or central retinal vein occlusion
- Diabetic macular edema

- Dexamethasone punctum insert (Dextenza® 0.4 mg) for the treatment of inflammation and pain following ophthalmic surgery and for the treatment of ocular itching associated with allergic conjunctivitis.

[a]*Refer to Exclusions for use as prophylactic when undergoing cataract surgery*

Exclusions:
- A fluocinolone acetonide intravitreal implant 0.59 mg (Retisert®) or 0.19 mg (Iluvien®) or dexamethasone intravitreal implant 0.7 mg (Ozurdex™) is considered **investigational** for the treatment of:
  - Birdshot retinochoroidopathy
  - Cystoid macular edema related to retinitis pigmentosa
  - Idiopathic macular telangiectasia type 1
  - Postoperative macular edema
  - Circumscribed choroidal hemangiomas
  - Proliferative vitreoretinopathy
  - Radiation retinopathy
  - Prophylaxis of cystoid macular edema in patients who meet both of the following:
    - Noninfectious intermediate uveitis or posterior uveitis
    - Cataract undergoing cataract surgery[b]
- All other uses of a corticosteroid intravitreal implant or punctum insert.

[b]*Refer to Inclusions for use in the absence of cataract surgery*

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

67027 67028 68841 J1096 J7311 J7312 J7313

J7314

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

NON-INFECTIOUS UVEITIS

Intravitreal Fluocinolone Acetonide Implant (0.59 mg)

Pivotal Trials

Two double-blind, randomized trials were conducted in patients with chronic (≥1-year history) noninfectious uveitis affecting the posterior segment of 1 or both eyes. The primary efficacy end point in both trials was the uveitis recurrence rate. These trials randomized patients to a fluocinolone acetonide 0.59-mg or to 2.1-mg implant. In 2004, the Food and Drug Administration (FDA) approved only the 0.59-mg dose and its approval was based on comparison of rates of recurrence of uveitis affecting the posterior segment of the study eye in the 34-week period post-implantation compared to the rates of recurrence in the 34-week period pre-implantation. Data from 224 patients were included.(3) Subsequently, FDA reported recurrence rates 1, 2, and 3 years post-implantation. Results are summarized in Table 1.

Table 1. Summary of Results From the FDA Pivotal Trial in Noninfectious Posterior Uveitis

Time Point	Uveitis Recurrence Rates, n (%)[a,b]	
	Study 1 (n=108)	Study 2 (n=116)
34 weeks preimplant	58 (53.7)	46 (39.7)
34 weeks postimplant	2 (1.8)	15 (12.9)
1 year postimplant	4 (3.7)	15 (12.9)
2 years postimplant	11 (10.2)	16 (13.8)
3 years postimplant	22 (20.4)	20 (17.2)
3 years postimplant[c]	33 (30.6)	28 (24.1)

Adapted from Bausch & Lomb (2012).[3]
FDA: Food and Drug Administration.
[a] Recurrence of uveitis for all postimplantation time points was compared with the 34-week preimplantation time point.
[b] p<.01.
[c] Results presented include imputed recurrences. Recurrences were imputed when a subject was not seen within 10 weeks of his or her final scheduled visit.

Jaffe et al (2006) results of one of the pivotal trials.(4) These trials are not discussed in detailed because the comparator was a non-approved dose of fluocinolone acetonide. Briefly, the two trials randomized 278 patients and 239 patients to a fluocinolone acetonide 0.59-mg or 2.1-mg implant, respectively. Pooled data from both doses in the first trial showed a reduction in recurrence rates in implanted eyes compared with an increase in recurrence in non-implanted eyes. An increase (~ 6 mm Hg) in intraocular pressure (IOP) and cataracts were observed in implanted eyes compared to non-implanted eyes. The second trial was not published and results reported in FDA documents (5) and results were similar to the first trial.

Additional Randomized Controlled Trials

Pavesio et al (2010) reported results of an industry-sponsored, open-label trial in which 140 patients with chronic noninfectious posterior uveitis were randomized to the fluocinolone acetonide 0.59-mg implant (n=66) or systemic corticosteroid therapy (and immunosuppression when indicated; n=74).(6) To be included in the trial, subjects had to have at least a 1-year history of recurrent uveitis. The primary efficacy outcome was time to first recurrence of uveitis. Patients in whom tapering of adjunctive anti-inflammatory therapy was insufficient despite receiving the implant were referred to as imputed or inferred failures. Results were therefore presented as both true recurrences and true plus inferred recurrences. When inferred recurrences were censored (11 subjects removed from the at-risk population), Kaplan-Meier analysis showed a significant decrease in the time to uveitis recurrence (6.3 months for 12 failures vs 7.0 months for 44 failures). When all subjects were included in the analysis, time to uveitis recurrence did not differ statistically (p=0.07). The relative risk (RR) of recurrence of uveitis was reduced by 71% with implants compared to standard therapy (RR=0.29; 95% confidence interval [CI], 0.14 to 0.59; 132 eyes).(7) Secondary efficacy outcomes included visual acuity improvement. Visual acuity in the implant group decreased after the surgery and again in the 15- to 18-month interval as a result of cataracts, then returned to baseline levels at

24 months, following extraction of the cataracts. Visual acuity in the systemic corticosteroid group remained consistent over the 2-year study.

The Multicenter Uveitis Steroid Treatment Trial (2010), sponsored by the National Eye Institute, is a partially blind randomized controlled trial (N=255) designed to compare visual acuity at 2 years with fluocinolone acetonide implants to systemic corticosteroid therapy (and immunosuppression when indicated) in patients with intermediate, posterior, or panuveitis.(8) Assessment of the primary outcome measure of best-corrected visual acuity (BCVA) using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart was blinded. After 24 (8) and 54 months (9) of follow-up, the vision improvements from baseline in the implant groups compared to the systematic therapy group were not statistically significant (+6.0 and +3.2 letters, p=.16; +2.4 and 3.1 letters; p=.073, respectively). Notably, approximately 21% of patients in the systemic group had received an implant by 54 months. At 24 and 54 months, the proportion of patients with a minimally important improvement did not differ significantly for any of the quality of life metrics (results not shown).(8,10) Patients receiving systemic therapy (in which corticosteroid-sparing immunosuppressive therapy was used to minimize ongoing use of prednisone to <10 mg/d for the large majority of patients) were associated with relatively little additional systemic morbidity compared with implant therapy. Systemic adverse events were infrequent in both groups. At 2 years, the proportion of patients with systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg at any visit was lower in the implant group than in the systemic group (13% vs 27%; hazard ratio [HR], 0.44; p=0.030), but the rate of antihypertensive treatment initiation did not differ substantially between the 2 groups (5% vs 11%; HR, 0.40; p=0.13), respectively. The incidences of other adverse systemic outcomes, including hyperlipidemia, diabetes, osteoporosis, fractures, and blood count/chemistry abnormalities, were not statistically distinguishable between groups (data not shown). Weight was stable over time in both groups.

Systematic Reviews

Brady et al (2016) reported results of a Cochrane review of RCTs comparing fluocinolone acetonide or dexamethasone intravitreal implants with standard therapy with at least 6 months of follow-up post treatment.(7) The primary outcome was recurrence of uveitis. Selected trials enrolled patients of all ages who had chronic noninfectious posterior uveitis, intermediate uveitis, or panuveitis with vision that was “better than hand motion.” Two trials, Pavesio et al (2010) (6) and Kempen et al (2011),(8) were included and judged to be of moderate quality (both are discussed above). Because the two trials were designed to answer different questions (one measured recurrence, one visual acuity), reviewers did not combine efficacy data. However, they did perform a meta-analysis of common side effects, which showed increased risks of needing cataract surgery (RR=2.98; 95% CI, 2.33 to 3.79; 371 eyes) and surgery to lower IOP (RR=7.48; 95% CI, 3.94 to 14.19; 599 eyes) in the implant group compared with the standard therapy group through 2 years of follow-up. Reviewers were unable to conclude that the implants were superior to traditional systemic therapy for the treatment of noninfectious uveitis. An update of the Cochrane review in 2023 by Reddy et al incorporated 2 additional studies to their analysis, but their conclusions were unchanged. (95)

Adverse Events

As listed in the prescribing label, nearly all phakic patients who receive implants are expected to develop cataracts and require cataract surgery.(3) Further, 75% of patients may experience elevated IOP and/or glaucoma severe enough to require IOP-lowering medications and 35% filtering surgeries. Separation of implant components is another potential complication and 6-

year cumulative risk of a spontaneous dissociation is 4.8% (95% CI, 2.4% to 9.1%).(11) Late-onset endophthalmitis is also a recognized as a surgical complication of intraocular implants.

Section Summary: Intravitreal Fluocinolone Acetonide Implant (0.59 mg) for Noninfectious Uveitis

Four RCTs have established the efficacy of fluocinolone acetonide implants (0.59 mg) for patients with noninfectious intermediate or posterior uveitis. Two of the four RCTs compared two doses of implants and two trials compared implants with systemic steroids (and immunosuppression when indicated). All trials supported the efficacy of fluocinolone acetonide intravitreal implants in preventing recurrence and improving vision over a four-year follow-up. The head-to-head trial comparing implants with systemic corticosteroids did not show substantial superiority in the overall effectiveness of either approach. The major limitation of these implants is nearly all phakic patients will develop cataracts and will require cataract surgery. Further, most will also develop glaucoma, with 75% patients requiring IOP-lowering medications and 35% requiring filtering surgeries.

Intravitreal Dexamethasone Implant (0.7 mg)

The evidence for dexamethasone intravitreal implants consists of a pivotal, double-blind RCT (HURON).(12) In this 8-week, manufacturer-sponsored, multicenter trial (46 study sites in 18 countries), 229 patients with noninfectious intermediate or posterior uveitis were randomized to 0.7-mg implants (n=77), 0.35-mg implants (n=76), or sham procedure (n=76). The primary outcome measure was the proportion of eyes with a vitreous haze score of 0 (no inflammation) at week eight. At baseline, the mean vitreous haze score was approximately +2 (moderate blurring of the optic nerve head). At eight weeks post treatment, the proportion of eyes with a vitreous haze score of 0 was 47% with the 0.7-mg implant and 12% with the sham procedure. At eight weeks, visual acuity, as assessed by gain of 15 or more letters in BCVA from baseline, was achieved by 40% of patients who received implants compared to 10% who received sham control. The incidences of elevated IOP (≥25 mm Hg) and cataracts in phakic eyes were higher in 0.7-mg implant-treated eyes versus sham control eyes (7.1% vs 4.2% and 15% vs 7%, respectively). Unlike the fluocinolone acetonide 0.59-mg implant, the long-term efficacy and safety data for the dexamethasone 0.7-mg implant is not available. Lightman et al (2013) reported 26-week data for vision-related functioning using National Eye Institute-Visual Function Questionnaire from HURON trial.(13) Using the distribution- and anchor-based methods, the authors reported that a clinically meaningful change for the National Eye Institute - Visual Function Questionaire-25 composite score was 3.86 and 10 points, respectively. Others have reported that range changes of 2.3 to 3.8 units in the composite score are meaningful.(14) In the HURON trial, the proportion of patients with a five or more point improvement in composite score at week 26 was 58% (42/73) in the 0.7-mg implant group versus 32% (24/74) in the sham-controlled arm ($p<0.05$).

Adverse Events

As listed in the prescribing label, in controlled studies, the most common adverse reactions reported by 20% to 70% of patients were cataract, increased IOP, and conjunctival hemorrhage.(15)

Section Summary: Intravitreal Dexamethasone Implant (0.7 mg) for Noninfectious Uveitis

One RCT comparing two doses of implants with sham-control has supported the efficacy of dexamethasone implants (0.7 mg) for patients with noninfectious intermediate or posterior

uveitis. Results of this trial have demonstrated the efficacy of the dexamethasone 0.7-mg implant in reducing inflammation and resulted in clinically meaningful improvements in vision at week eight compared to sham controls. Further, at week 26, patients treated with implants reported meaningful improvements in vision-related functioning. The major limitation of this trial was its lack of long-term follow-up. Further, as a class effect, use of dexamethasone implants resulted in higher incidences of cataracts and elevated intraocular pressure (IOP).

Intravitreal Fluocinolone Acetonide Implant (0.18 mg, Yutiq)
Jaffe et al (2019) assessed the safety and efficacy of an intravitreal fluocinolone acetonide (0.18 mg) insert to manage inflammation associated with chronic noninfectious posterior uveitis.(16) A multicenter, randomized, prospective, doubled-masked, sham-controlled, three-year phase III clinical trial included one hundred twenty-nine participants with recurrent noninfectious posterior uveitis who were assigned randomly to fluocinolone acetonide insert (n = 87) or sham injection (n = 42). The more severely affected eye in participants with bilateral disease was designated as the study eye. The insert (fluocinolone acetonide, 0.18 mg) was injected into the vitreous cavity; sham injection mimicked the insert delivery procedure. Ophthalmic examinations, optical coherence tomography, and ocular tolerability and discomfort assessments were conducted; study visits were on days 7 and 28 and months 2, 3, 6, 9, and 12. Uveitis recurrence was treated as needed. The six-month recurrence rate was the primary outcome measure. The 6-month (28% and 91%) and 12-month (38% and 98%) uveitis recurrence rates were significantly lower ($P < .001$) with fluocinolone acetonide insert vs. sham, respectively. Fewer recurrences per study eye (mean, 0.7 vs. 2.5), lower incidence of 15-letter or more decrease in best-corrected visual acuity (14% vs. 31%), and reduced systemic (19% vs. 40%) and local (7% vs. 62%) uveitis adjunctive treatments were observed with fluocinolone acetonide insert vs. sham, respectively. The fluocinolone acetonide insert group showed higher rates of cataract. Intraocular pressure-lowering treatment use was similar between groups. No deaths, treatment-related study discontinuations, or unanticipated safety signals were observed through 12 months. Authors concluded that chronic noninfectious posterior uveitis was managed successfully in this study population. Fluocinolone acetonide insert eyes experienced fewer uveitis recurrence episodes, required fewer adjunctive treatments, and demonstrated less visual acuity loss compared with sham eyes.

Cai et al (2020) reported on the long-term effect of intravitreal fluocinolone acetonide implantation (0.18 mg) in noninfectious uveitis.(17) A retrospective study of patients with at least 12 months of follow-up who had completed a two-year prospective, investigational new drug study with 0.18-mg fluocinolone acetonide insert recorded time to uveitis recurrence or cystoid macular edema (CME) post insertion. Twelve eyes from 12 participants (mean age 43 years, range 25-64 years) were included. Patients were followed for a mean of 34.2 months (range, 12.0-56.9 months) after completion of the prospective trial. Five eyes (42%) did not have a documented uveitis recurrence or CME occurrence. Five eyes (42%) had a uveitis recurrence with the mean time to recurrence 36.1 months (range, 22.8-61.one months) after intravitreal fluocinolone acetonide implantation. Two eyes (16%) had CME alone, the mean time to occurrence 36.9 months (range 36.1-42.1 months). On Kaplan-Meier analysis, the estimated probability of remaining recurrence-free 36 months after intravitreal fluocinolone acetonide implantation was 0.67 (95% confidence interval, 0.34-0.86). Authors concluded that clinical trial data suggest that the injectable intravitreal fluocinolone acetonide for noninfectious uveitis can provide control for three years on average. These long-term data support the use of intravitreal fluocinolone acetonide to control noninfectious uveitis.

Section Summary: Intravitreal Fluocinolone Acetonide Implant (0.18 mg, Yutiq)

Two studies have established the efficacy and long term effect of fluocinolone acetonide implants (0.18 mg) for patients with noninfectious uveitis. One study demonstrated the superiority of implants over sham controls. The 6-month and 12-month uveitis recurrence rates were significantly lower when treated with intravitreal fluocinolone acetonide implant (0.18 mg Yutiq). Implant-treated eyes showed clinically meaningful improvements in controlling uveitis recurrence for three years, on average, post implant. The major limitation of these implants is that patients are more likely to develop cataracts and require cataract surgery.

MACULAR EDEMA AFTER RETINAL VEIN OCCLUSION

Intravitreal Dexamethasone (0.7 mg)

Systematic Reviews

The American Academy of Ophthalmology published a technology assessment (2015) on therapies for macular edema associated with central retinal vein occlusion.(18) The Academy identified four clinical trials that provided level I evidence supporting the use of anti-vascular endothelial growth factor (anti-VEGF) pharmacotherapies and two clinical trials providing level I evidence for intravitreal corticosteroid injection with the dexamethasone intravitreal implants or triamcinolone. Evidence on the safety and efficacy of other reported interventions was of lesser strength. The assessment noted that evidence on long-term efficacy of corticosteroid treatments is limited and that intravitreal corticosteroids led to a higher frequency of adverse events including cataract and IOP elevation compared with anti-VEGF treatments. There are limited data on combination therapy with anti-VEGF and corticosteroid injections compared with monotherapy.

A Bayesian network meta-analysis of the efficacy and safety of treatments for macular edema secondary to branch retinal vein occlusion was published in 2015.(19) Eight RCTs (total n=1743 patients) were included; patients were treated with ranibizumab as needed, aflibercept monthly, dexamethasone implant, laser photocoagulation, ranibizumab plus laser, or sham intervention. The probability of being the most efficacious treatment, based on letters gained, or for a gain 15 letters or more, was highest for monotherapy of anti-VEGF treatments (30%-54% probability), followed by ranibizumab plus laser, and lowest (0%-2% probability) for the dexamethasone implant, laser, or sham treatment. Treatment with ranibizumab resulted in an average increase of 8 letters compared with the dexamethasone implant. Patients treated with the dexamethasone implant had statistically significant higher rates of ocular hypertension than patients given anti-VEGF monotherapy (odds ratio, 13.1). In 2017, the American Academy of Ophthalmology published a technology assessment on therapies for macular edema associated with branch retinal vein occlusion.22, In the assessment, they identified 10 trials providing level 1 evidence supporting the use of anti-VEGF therapy and 6 trials providing level 1 evidence supporting the use of intravitreal corticosteroids, including triamcinolone (4 trials) and dexamethasone (2 trials). They concluded that based on the available evidence, intravitreal pharmacotherapy with anti-VEGF products is effective and safe for macular edema secondary to branch retinal vein occlusion. Additionally, intravitreal corticosteroids on their own are effective and safe for the management of macular edema, although corticosteroids are associated with increased potential ocular adverse events. (96)

Randomized Controlled Trials

Data presented to the FDA for the dexamethasone intravitreal implant (Ozurdex™) were from two, six-month, double-masked RCTs called GENEVA (167 clinical sites in 24 countries).(1,20) A six-month open-label extension of these two pivotal trials was reported in 2011.(1,2) A total

of 1267 patients who had clinically detectable macular edema associated with either central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO) were randomized to a single treatment with a dexamethasone 0.7 mg implant (n=427), dexamethasone 0.35 mg implant (n=414), or sham control (n=426). The primary outcome measure was time to achieve a 15-or-more letter improvement in BCVA. A secondary outcome was the proportion of eyes achieving a 15-or-more letter improvement from baseline at 180 days. In individual studies and pooled analysis, time to achieve a 15-or-more letter (3-line) improvement in BCVA was significantly faster with implants than with sham (p<.01) (data not shown). As evident from Table 2, the proportion of patients with a 15-or-more letter improvement from baseline in BCVA was higher in the implant with the FDA-approved dose (0.7 mg) than with sham for the first three months. There was no significant difference in the proportion of patients who improved by 15 letters or more at six-month follow-up. Note that the implant lasts for six months.

Table 2. Summary of Results From the FDA Pivotal Trial in Retinal Vein Occlusion

Time Point	Patients With ≥15 Letters Improvement From Baseline in BCVA, N (5)					
	Study 1			Study 2		
	Implant (0.7 mg)	*Sham*	*p*	*Implant (0.7 mg)*	*Sham*	*p*
Day 30	40 (20)	15 (7)	<0.01	51 (23)	17 (8)	<0.01
Day 60	58 (29)	21 (10)	<0.01	67 (30)	27 (12)	<0.01
Day 90	45 (22)	25 (12)	<0.01	48 (21)	31 (14)	0.039
Day 180	39 (19)	37 (18)	0.780	53 (24)	38 (17)	0.087

Adapted from Allergan (2014).[15]
BCVA: best-corrected visual acuity; FDA: Food and Drug Administration.

Additional Studies

Several additional RCTs have evaluated the comparative effects of dexamethasone intravitreal implants to other therapies and found mixed results.(19-25). In the largest trial, Kuppermann et al (2007) reported results for an RCT in which 315 patients with persistent macular edema of different etiology (diabetic retinopathy [n=172], BRVO [n=60], CRVO [n=42], uveitis [n=14], or post–cataract surgery macular edema [n=27]) were assigned to the dexamethasone 0.35-mg implant, the dexamethasone 0.7-mg implant, or observation.(22) At six months, the proportion of patients meeting the primary outcome of an improvement in visual acuity of 10 letters was 24%, 35% and 13% in 0.35-mg implants, 0.7-mg implants, and observation-only groups, respectively. In a small trial in 50 patients, Pichi et al (2014) found that the combination of dexamethasone 0.7-mg intravitreal implants plus macular grid laser increased both visual acuity and the interval between repeated implants.(19) Gado and Macky (2014; n=60) reported no significant differences in visual acuity outcomes between dexamethasone implants and bevacizumab.(21) Maturi et al (2014) reported on results for 30 patients randomized to dexamethasone implants plus bevacizumab or to bevacizumab monotherapy and found no additional benefit for visual acuity with the combination treatment at six months.(20) Compared to antivascular endothelial growth factor for treatment of macular edema after branch retinal vein occlusion, a meta-analysis by Ji et al (2019) of six studies (one RCT, four retrospective studies, one prospective study; N=452 eyes) found similar best corrected visual acuity change at three or six months with dexamethasone intravitreal implants (0.7 mg), but a higher risk of intraocular pressure elevation for dexamethasone treatment.(24) In another 60 patients with macular edema following branch retinal vein occlusion from a single-center in New Delhi, a randomized, open-label trial by Kumar et al (2019) found that best-corrected visual acuity gains at six months for 0.7 mg dexamethasone intravitreal implants, with or without laser photocoagulation (+9.50 and +10.50, respectively), were similar to intravitreal ranibizumab

(one injection of 0.5 mg) with laser photocoagulation (+10.00), but lower than for three injections of 0.5 mg ranibizumab without laser photocoagulation (+18.00).(23)

For the comparison to triamcinolone, evidence includes the open-label multicenter PeriOcular vs. INTravitreal corticosteroids for uveitic macular edema (POINT; NCT02374060) trial by Thorne et al (2019), in which 192 patients with macular edema, defined as a central subfield thickness two standard deviations greater than the population normative mean, were randomized to receive periocular triamcinolone acetonide 40 mg, intravitreal triamcinolone acetonide 4 mg, or the 0.7 mg intravitreal dexamethasone implant.(25) Retreatment was permitted for the triamcinolone treatments at eight weeks and at 12 weeks for dexamethasone. Proportion of eyes with macular edema resolution varied between treatments at eight weeks (61% for dexamethasone, 47% for intravitreal triamcinolone, 20% for periocular triamcinolone) but not at 24 weeks (41%, 36%, and 35%, respectively). Change in best-corrected visual acuity was similar for intravitreal dexamethasone, intravitreal triamcinolone and periocular triamcinolone at eight weeks (+9.53 vs. +9.70 vs. +4.37 letters) and 24 weeks (+9.21 vs. +9.60 vs. +4.07). The main limitation was that, at 24 weeks, follow-up was relatively short-term. Longer-term data will be needed to confirm these findings.

An open-label, prospective, real-world study evaluated the effectiveness of dexamethasone intravitreal implant (0.7 mg) ina subgroup of patients with treatment-naïve diabetic macular edema Fraser-Bell et al (2021). (83) Of the 200 eyes enrolled in the original AUSSIEDEX study, 57 were treatnaïvenaive. Changes in mean best-corrected visual acuity and central subfield retinal thickness from baseline to 52 weeks in this subgroup were +3.4 letters (p=.042) and -89.6 micrometers(p<.001), respectively, with a mean of 2.5 injections of dexamethasone intravitreal implant 0.7 mg. The most common adverse event was increased intraocular pressure, with 20% of eyes requiring intraocular-pressure lowering medications.

An open-label, retrospective, 5-year real world study evaluated the effectiveness of dexamethasone intravitreal implant (0.7 mg) compared to anti-VEGF treatment in patients with diabetic macular edema secondary to retinal vein occlusion (Zhang et al 2022). (84) There were 16 patients included, with 8 patients in each group. At the end of the 5-year evaluation period, changes in the best-corrected visual acuity (0.69 ± 0.36 Logarithm of the Minimum Angle of Resolution (LogMAR) vs. 0.57 ± 0.30 LogMar; p=.574) and central macular thickness (183.25 ± 97.31 µm vs. 195.38 ± 40.92 µm; p=.442) were not significantly different between the dexamethasone and anti-VEGF groups, respectively. The dexamethasone group had a higher foveal avascular zone circularity index and higher retinal perfusion density than the anti-VEGF group.

Adverse Events
As listed in the prescribing label, in controlled studies, the most common adverse reactions reported by 20% to 70% of patients were cataracts, increased IOP, and conjunctival hemorrhage.(15)

Intravitreal Fluocinolone Acetonide Implant (0.59 mg)
No RCTs were identified assessing the fluocinolone acetonide implants for the treatment of macular edema following retinal vein occlusion.

Section Summary: Intravitreal Dexamethasone Implant (0.7 mg) or Intravitreal Fluocinolone Acetonide Implant (0.59 mg) for Macular Edema After Retinal Vein Occlusion

Two identical RCTs have established the efficacy of dexamethasone intravitreal implants (0.7 mg) for patients with macular edema following retinal vein occlusion. The two RCTs compared two doses of implants with a sham control. Compared to sham, both doses of the dexamethasone implant resulted in clinically meaningful improvements in visual acuity within one to three months post-implantation. Further, implant-treated patients achieved improvement in vision faster than the sham controls. However, the vision gain was similar at six months. Several additional RCTs and a meta-analysis have evaluated the comparative effects of dexamethasone intravitreal implants versus other therapies and found mixed results. A few notable findings include that the combination of implants with macular grid laser may increase the interval between repeated implants and dexamethasone intravitreal implants may have similar efficacy to other types of treatments. Further, as a class effect, use of dexamethasone implants resulted in higher incidences of cataracts and elevated IOP.

No trials assessing the use of fluocinolone acetonide implants were identified.

DIABETIC MACULAR EDEMA

Rittiphairoj et al (2020) published a Cochrane review that evaluated the efficacy of intravitreal steroids for macular edema in diabetes. (81) It is an update of the previously published Cochrane review by Grover et al (2008). (26) Ten trials were included, involving 4505 eyes with diabetic macular edema. Among those, 4 trials examined the effectiveness of intravitreal steroid implantation with fluocinolone acetonide (Retisert) or the dexamethasone drug delivery system compared with sham or an anti-vascular endothelial growth factor agent (all discussed below) and 6 examined triamcinolone. Cochrane reviewers concluded that, compared to sham or control, intravitreal steroids may improve visual outcomes in people with diabetic macular edema, but that these benefits should be weighed against risk of intraocular pressure elevation.

Intravitreal Fluocinolone Acetonide Implant (0.59 mg)

Systematic Reviews

Rittiphairoj et al (2020) published a Cochrane review that evaluated the efficacy of intravitreal steroids for macular edema in diabetes. (85) It is an update of the previously published Cochrane review by Grover et al (2008). (26) Ten trials were included, involving 4505 eyes with diabetic macular edema. Among those, 4 trials examined the effectiveness of intravitreal steroid implantation with fluocinolone acetonide (Retisert) or the dexamethasone drug delivery system compared with sham or an anti-VEGF agent (all discussed below) and 6 examined triamcinolone. Cochrane reviewers concluded that, compared to sham or control, intravitreal steroids may improve visual outcomes in people with diabetic macular edema, but that these benefits should be weighed against the risk of intraocular pressure elevation.

Randomized Controlled Trials

Pearson et al (2011) reported on the three-year efficacy and safety results of an industry-sponsored, single-blind (evaluator) RCT in which 196 patients with persistent or recurrent unilateral or bilateral DME (referred to as refractory DME) were randomized to fluocinolone acetonide implants (0.59 mg) (n=127) or standard of care, defined as additional laser as needed after six months or observation (n=69).(27) All patients had received focal/grid laser photocoagulation prior to randomization. At six months, the proportions of patients who received laser retreatment in implant and standard of care groups were 4% and 13%, respectively; the percentages after three years of follow-up were 15% and 41%, respectively. The primary efficacy outcome, (≥ 15-letter improvement in BCVA at 6 months before any

additional laser treatment) was achieved in 16.8% of implanted eyes versus 1.4% of standard of care eyes (p<.05). Between six and 24 months, visual acuity was statistically significant in favor of the implant group but not beyond 30 months. At three years, there was no significant difference between the groups (eg, 31.1% of implanted eyes vs 20.0% of standard of care eyes improved ≥15 letters at three years). As expected, there were higher incidences of elevated IOP (≥30 mm Hg; 61.4% vs 5.8%), need for surgery to treat glaucoma (33.8% vs 2.4%), and cataracts extraction in phakic eyes (91% vs 20%), respectively, for eyes treated with implants compared to standard of care. The incidence of vitreous hemorrhage (40.2% vs 18.8%), pruritus (38.6% vs 21.7%), and abnormal sensation in the eye (37.0% vs 11.6%), respectively, were also higher in the eyes treated with implants versus standard of care.

Section Summary: Intravitreal Fluocinolone Acetonide Implant (0.59 mg) for Diabetic Macular Edema

One RCT comparing fluocinolone acetonide implants (0.59 mg) with standard of care (as needed laser or observation) has supported the efficacy of implants for patients with DME. The primary efficacy outcome, at least a 15-letter improvement in BCVA was significantly improved in a greater proportion of patients given implants versus laser at all time points assessed, except at or beyond 30 months. Note that this implant is active for 30 months. As a class effect, in patients with phakic eyes, use of implants resulted in 90% requiring cataract surgery and 60% developing elevated IOP. Due to the substantial increase in adverse events and availability of agents with safer tolerability profiles (eg, anti-Vascular Endothelial Growth Factor inhibitors [VEGF]), this implant is not indicated for diabetic macular edema.

Intravitreal Fluocinolone Acetonide Implant (0.19 mg)

Randomized Controlled Trials

Two double-blind, randomized trials (FAME) has assessed patients with DME previously treated with laser photocoagulation. The primary efficacy end point of both trials was the proportion of subjects in whom vision had improved by 15 letters or more at two years from baseline. These trials randomized patients to fluocinolone acetonide 0.19-mg or 0.5-mg implants or to sham. Results of these trials were published by Campochiaro et al (2011).(28) In 2014, FDA approved the 0.19-mg dose only based on similar efficacy at two years between the low and high dose in improving vision by 15 letters or more from baseline (data not shown).(29) Relevant results with FDA-approved dosing are summarized in Table 3. Campochiaro et al (2012) subsequently reported on three-year results.(30) The percentage of patients who gained 15 letters or more using the last observation carried forward was 28.7% in the implant group and 18.9% in the sham group. Results of sensitivity analysis without imputation for missing data (~70% follow-up) showed similar results; the percentages of patients who gained 15 letters or more in the two groups were 33.0% and 21.4%, respectively. Subgroup analysis showed greater improvement in visual acuity in patients who were pseudophakic compared to those who were phakic (difference in mean change in number of letters at two years from baseline was 5.6 in pseudophakic patients vs one letter in phakic patients).(29) This was due to loss of vision from cataracts in phakic eyes that was observed more frequently in eyes with implants versus sham controls. Subgroup analysis also showed greater efficacy in patients with chronic (≥3 years) compared with non-chronic (<3 years) DME.(31) The difference in the proportion of patients who gained 15 or more letters in the implant group versus the sham control group with chronic DME patients was 21% and -5.5 % among non-chronic DME patients.

Table 3. Summary of 2 Year Results from the FDA Pivotal Trials in Diabetic Macular Edema

Outcome	Study 1 (N=285)			Study 2 (N=276)		
	Implant (n=190)	*Sham (n=95))*	*Difference (95% CI)*	*Implant (n=186)*	*Sham (n=90)*	*Difference (95% CI)*
15 letters	51 (27)	14 (15)	12.1 (2.6 to 21.6)	57 (31)	16 (18)	13.0 (2.7 to 23.4)
↓ 15 letters	26 (14)	5 (5)	8.4 (1.8 to 15.1)	22 (12)	9 (10)	1.8 (-5.9 to 9.6)

Adapted from Alimera Sciences (2014).[23]
Values are n (%) or as otherwise indicated.
CI: confidence interval; FDA: Food and Drug Administration.

Massin et al (2016) reported the results of a small prospective noncomparative study in 16 patients with DME insufficiently responsive to laser and anti-VEGF who received fluocinolone acetonide 0.19-mg implants.(32) Two groups of patients were evaluated - group I (n=6) included patients ineligible anti-VEGF therapy who received previous treatment with laser photocoagulation while group II (n=10) included patients previously treated with laser photocoagulation and at least three monthly anti-VEGF treatments. Central subfield thickness was reduced by -299 µm in group I and -251 µm in group II at 12 months. Mean change in area under the curve from baseline to last value for all eyes was +4.2 letters in group I and +3.9 letters in group II. The benefit in BCVA letter score was more limited and heterogeneous (the effect was more pronounced in pseudophakic eyes) with some patients achieving high improvements of visual acuity, whereas others did not improve. Small number of patients and lack of a control arm limit the interpretation of these findings.

Adverse Events

As listed in the prescribing label, at the end of the three-year follow-up, 82% (192/235) of phakic eyes with implants underwent cataract surgery compared to 50% (61/121) receiving the sham control.(29) Among these patients, 80% of implant patients versus 27% of sham-controlled had cataract surgery, generally within the first 18 months of the trials. The proportion of patients with IOP elevation of 10 mm Hg or more from baseline was three times higher in the implant group (34%) versus the sham group (10%). Respective proportions of patients with IOP of 30 mm Hg or more were 20% and 4%, respectively. As a consequence, a higher proportion of patients in the implant group required surgery for glaucoma (5% vs 1%).

Section Summary: Intravitreal Fluocinolone Acetonide Implant (0.19 mg) for Diabetic Macular Edema

Two RCTs have established the efficacy of fluocinolone acetonide implants (0.19 mg) for patients with DME. Both trials demonstrated the superiority of implants over sham controls. Implant-treated eyes showed clinically meaningful improvements in the vision at two and three years post implant. Subgroup analysis showed greater improvements in visual acuity in patients who were pseudophakic than those who were phakic. The major limitation of these implants is that nearly 80% all phakic patients will develop cataracts and will require cataract surgery. Further, IOP was elevated in 34% of patients who received this implant compared with 10% of controls, leading to the restricted indication for patients, previously treated with corticosteroids, who do not have a clinically significant rise in IOP.

Intravitreal Dexamethasone Implant (0.7 mg)

Randomized Controlled Trials

Two double-blind, randomized trials have assessed patients with DME. These trials randomized patients to a 0.7-mg or to a 0.35-mg implant or a sham procedure. Retreatment was allowed if it was at least six months since the prior treatment and there was evidence of residual edema. The primary efficacy end point in both trials was the proportion of subjects in whom visual acuity had improved by 15 or more letters at 39 months from baseline or at the final visit for patients who exited the study at or prior to month 36. The month 39 extension was included to accommodate the evaluation of safety and efficacy outcomes for patients who received retreatment at month 36. Results of these trials were published by Boyer et al (2014).(33) In 2014, FDA approved the 0.7-mg dose.(15) Relevant results with FDA-approved dosing are summarized in Table 4. Only 14% of study patients completed the month 39 visit (16.8% from implant, 12.2% from sham). The visual acuity improvements from baseline increased during a treatment cycle, peaked at three months post-treatment and diminished after that (data not shown). This was due to loss of vision related to development of cataracts. Subgroup analysis showed greater improvements in visual acuity in patients who were pseudophakic than in those who were phakic (difference in mean change in number of letters at 39 months from baseline was 4.2 letters in pseudophakic patients vs 0.3 letters in phakic patients).(29)

Table 4. Summary of 39-Months Results From the FDA Pivotal Trials in Diabetic Macular Edema

Outcome	Study I (n=328)			Study II (n=328)		
	Implant (n=163)	*Sham (n=165)*	*Difference (95% CI)*	*Implant (n=165)*	*Sharm (n=163)*	*Difference (95% CI)*
15 letters	34 (21)	19 (12)	9.3 (1.4 to 17.3)	30 (18)	16 (10)	13.0 (2.7 to 23.4)
↓ 15 letters	15 (9)	17 (10)	-1.1 (-7.5 to 5.3)	30 (18)	18 (11)	7.1 (-0.5 to 14.7)

Adapted from Allergan (2014).[15]
Values are n (%) or as otherwise indicated.
CI: confidence interval; FDA: Food and Drug Administration.

Subsequent to the 2014 pivotal trials and FDA approval, several small and/or short-term trials and retrospective studies have been published that evaluate the comparative effects of intravitreal dexamethasone implant (0.7 mg) versus other treatments – primarily antivascular endothelial growth factor in various subgroups of patients with diabetic macular edema (Table 5).(33-38), In general, compared with primarily antivascular endothelial growth factor treatments, intravitreal dexamethasone implant (0.7 mg) was consistently associated with larger reductions in retinal thickness, but visual acuity changes were similar between treatment groups. While promising, as these findings are based on single small studies, several of which are nonrandomized, adequately-powered and longer-term randomized trials are still needed to confirm these findings.

Table 5. Summary of Additional Studies of Intravitreal Dexamethasone Implant (0.7 mg) in Diabetic Macular Edema

Author, Year, Study, Design, Sample Size	Population	Comparator	Summary of Findings
Gillies et al (2014), BEVORDEX RCT, N=88	Patients with DME	Bevacizumab	Dexamethasone had greater reduction in 12-mo retinal thickness and similar for BCVA improvement of ≥ 10 letters. But, dexamethasone resulted in greater risk of vision loss > 10 letters and more adverse events.

Sharma et al 2019, RCT, N=40	Centre involved DME (CiDME)	Bevacizumab 1.25 mg or ranibizumab 0.5 mg	Dexamethasone had greater improvements in 3-mo retinal thickness, but similar visual acuity
Unpublished RCT, NCT02471651, N=40	Persistent DME following anti-VEGF therapy	Continue on various anti-VEGF therapy	Treatments similar in 9-mo retinal thickness and visual acuity improvements

BCVA: best-corrected visual acuity; DME: Diabetic Macular Edema; NCT02471651: Dexamethasone Intravitreal Implant (0.7mg) for the Treatment of Persistent Diabetic Macular Edema Following Intravitreal Anti-Vascular Endothelial Growth Factor Therapy; RCT: randomized controlled trial; VEGF:vascular endothelial growth factor

Nonrandomized Studies

Cornish et al (2023) reported on 5-year outcomes of the BEVORDEX trial in patients with diabetic macular edema. (86) Patients were randomized to receive either intravitreal dexamethasone implant (0.7 mg) or intravitreal bevacizumab. Data was available for 82% (n=72) of eyes 3 years after enrollment, 72% (n=63) at 4 years, and 59% (n=52) at 5 or more years of follow-up. Baseline characteristics of the eyes from both study arms were similar. Several other nonrandomized trials have been published that evaluate the comparative effects of intravitreal dexamethasone implant (0.7 mg) versus other treatments. (35,36,37) Tables 6 and 7 summarize key characteristics and results of these trials.

Table 6. Summary of Key Nonrandomized Trials Study Characteristics

Study	Study Type	Country	Dates	Participants	Treatment 1	Treatment 2	Follow- Up
Cornish et al (2023)	Cohort	Australia	2010-NR	Patients with center-involving DME	Dexamethasone implant (0.7mg); n=46 eyes	Bevacizumab (1.25 mg); n=42 eyes	Up to 5 years or more
Bolukbasi et al (2019)	Retrospective comparative	Turkey	2017-2018	Patients who received treatment for naive DME with SRD	Dexamethasone implant (0.7mg); n=25 eyes	Intravitreal aflibercept injections (2 mg); n=32 eyes	3 months
Cakir et al (2019)	Retrospective comparative	Turkey	2017-2018	Treatment-naive DME patients with ERM	Dexamethasone implant (0.7mg); n=22 eyes	Intravitreal ranibizumab (0.5mg); n=17 eyes	4 months
Coelho et al (2019)	Retrospective comparative	Portugal	NR	Patients with prior fluocinolone acetonide and/or dexamethasone treatment for DME	Dexamethasone implant (0.7mg); n=17 eyes	Fluocinolone acetonide (0.19mg); n=29 eyes	Up to 24 months of follow-up

DME: Diabetic Macular Edema; ERM, epiretinal membrane; NR: not reported; SRD, serous retinal detachment.

Table 7. Summary of Key Nonrandomized Trials Study Results

Study	Mean VA at 5 years, letters (95% CI)	Proportion of eyes who gained ≥10 letters from baseline to 5 years, n (%)	Mean change in CMT, µm	Proportion of eyes that had cataract surgery by 5 years (%)

Cornish et al (2023)			From baseline to 5 years (95% CI)	
Dexamethasone	58.5 (95% CI, 55.1 to 61.9)	14 (30.4%)	−150 (95% CI, −199 to −100)	84%
Bevacizumab	59.5 (95% CI, 57.4 to 63.6)	14 (33.3%)	−173 (95% CI, −232 to −121)	68%
Bolukbasi et al (2019)	Mean BCVA at 3 months		Mean change in CMT (+/- SD), µm	
Dexamethasone	0.4 ± 0.2 LogMAR	NR	228.6 ± 109.8	NR
Aflibercept	0.3 ± 0.2 LogMAR	NR	168.5 ± 106.4	NR
Cakir et al (2019)	Mean BCVA at 4 months	Mean change in CMT (+/- SD), µm at 1 month	Mean change in CMT (+/- SD), µm at 4 months	Proportion of eyes that had cataract surgery by end of study
Dexamethasone	1.0 ± 0.5 LogMAR	188.2 ± 142.7	−63 ± 67.3	0
Ranibizumab	0.7 ± 0.5 LogMAR	95.7 ± 110.7	−5.8 ± 43.9	0
Coelho et al (2019)		Letter improvement on ETDRS chart	CFT reduction, µm	
Dexamethasone	NR	>5-letter improvement on the ETDRS chart at months 1 and 3	>100 µm CFT reduction at month 1	NR
Fluocinolone acetonide	NR	>10-letter improvement on the ETDRS chart over months 3 to 24	Sustained ~200 µm over 1 to 24 months	NR

BCVA, best corrected visual acuity; CI: confidence interval; CFT: central foveal thickness; CMT, central macular thickness; CI: confidence interval; ETDRS: Early Treatment Diabetic Retinopathy Study; logMAR: logarithm of the minimum angle of resolution; NR: not reported; SD, standard deviation; VA: visual acuity.

Section Summary: Intravitreal Dexamethasone Implant (0.7 mg) for Diabetic Macular Edema

Two identical RCTs have established the efficacy of dexamethasone intravitreal implants (0.7 mg) for patients with DME. The 2 RCTs compared 2 doses of implants with a sham control. Compared to sham, both doses of the dexamethasone implant resulted in clinically meaningful improvements in visual acuity at 39 months post-implantation. The visual acuity improvement peaked at 3 months post-treatment but diminished after that, possibly due to development of cataracts. Subgroup analysis showed greater improvements in visual acuity in patients who were pseudophakic than in those who were phakic. Evidence from various small and/or short-term trials have found that, compared with primarily antivascular endothelial growth factor treatments, intravitreal dexamethasone implant (0.7 mg) was consistently associated with larger reductions in retinal thickness, but visual acuity changes were similar between treatment groups.

Intravitreal Dexamethasone Implant (0.7 mg) Plus Antivascular Endothelial Growth Factor Therapy

Clinical Context and Test Purpose

The purpose of intravitreal dexamethasone implant (0.7 mg) plus antivascular endothelial growth factor therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as standard therapy, in patients with diabetic macular edema.

The following PICO was used to select literature to inform this review.

Patients

The relevant population of interest is individuals with diabetic macular edema.

Interventions

The intervention of interest is intravitreal dexamethasone implant (0.7 mg) plus antivascular endothelial growth factor therapy.

Comparators

The comparator of interest is standard of care.

Outcomes

The beneficial outcomes of interest are symptom improvement, change in disease status, functional status and quality of life. Harmful outcomes of interest are treatment-related morbidity. Follow-up over the first few weeks following surgery is of interest for relevant outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

1. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
2. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
3. To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
4. Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Randomized Controlled Trials

For individuals with diabetic macular edema who receive an intravitreal dexamethasone implant (0.7 mg) plus antivascular endothelial growth factor therapy, the evidence includes two small randomized controlled trials of 169 patients (n range, 40-129) (Table 8).(34,39) The first RCT, published by Maturi et al (2015), was single-blinded and used bevacizumab as the antivascular endothelial growth factor treatment.(39) The second RCT, published by Maturi et al (2018) was double-blinded, used ranibizumab as the antivascular endothelial growth factor treatment, and focused on a ranibizumab-resistant population with persistent diabetic macular edema despite previous treatment.(34) Findings from both trials (Table 7) were consistent in demonstrating that although adding dexamethasone to an antivascular endothelial growth factor treatment can lead to a greater mean reduction in central subfield thickness, it does not improve visual acuity and can lead to a higher risk of intraocular pressure elevation. The main limitations of both RCTs (Tables 10 and 11) were their small sample size and the relatively short-term follow-up in the 2018 RCT. Based on the consistent lack of improvement in visual acuity, increased risk of intraocular pressure elevation, and imprecision, these RCTs provide

insufficient evidence to determine that the technology results in a meaningful improvement in the net health outcome.

Table 8. Summary of Key RCT Characteristics

Study, Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	*Comparator*
Maturi et al (2018)	U.S.	40	2014-2016	Persistent DME, with visual acuity of 20/32 to 20/320 after at least 3 anti-VEGF injections	Dexamethasone 0.7 mg + continued 0.3-mg ranibizumab, N=65 eyes	Sham + continued 0.3-mg ranibizumab, N=64
Marturi et al (2015)	U.S.	1	NR	DME with a CST of.250 mm measured by time-domain optical coherence tomography	Bevacizumab 1.25 mg intravitreally at baseline + dexamethasone 0.7 mg implant at the 1-mo visit, N=21	Bevacizumab 1.25 mg intravitreally at baseline and Mo 1, N=19

CST: central subfield thickness; DME: Diabetic Macular Edema; VEGF: vascular endothelial growth factor; mg: milligrams; NR: Not Reported; RCT: randomized controlled trial.

Table 9. Summary of Key RCT Results

Study	Mean improvement in visual acuity (SD), letters	Mean change in central subfield thickness (SD), µm	Increased intraocular Pressure
Maturi et al (2018)[a]	127	127	127
Dexamethasone + continued ranibizumab	+2.7 (9.8)	-110 (86)	19 (29%)
Sham + continued ranibizumab	+3.0 (7.1)	-62 (97)	0
MD (95%CI)	-0.5 (-3.6 to 2.5)	-52 (-82 to -22)	P<0.001
Maturi et al (2015)[b]	35	35	35
Dexamethasone + Bevacizumab	+5.4 (10.7)	-45 (107)	6 (33%)
Bevacizumab monotherapy	+4.9 (12.3)	-30 (100)	1 (5.9%)
P-value	0.9	0.03	NR

CI: confidence interval; MD: mean difference; NR: Not Reported; RCT: randomized controlled trial; SD: Standard deviation.
a 24-weeks.
b 12 months.

Table 10. Study Design and Conduct Limitations

Study	Allocation[a]	Binding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Maturi et al (2018)					4. Sample size lower than needed for 90% power	
Maturi et al (2015)	3. Unclear	1. Patients not blinded			1. Not reported	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias. 5. Inadequate description of methods
b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference. 4. Insufficient power
f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Table 11. Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-up[e]
Maturi et al (2018)					1. 24 wks is a relatively short follow-up
Maturi et al (2015)					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
a Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other. b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Section Summary: Intravitreal Dexamethasone Implant (0.7 mg) Plus Antivascular Endothelial Growth Factor Therapy for Diabetic Macular Edema

Two small RCTs have consistently demonstrated that although combined treatment with dexamethasone implants plus an antivascular endothelial growth factor treatment can lead to a greater mean reduction in central subfield thickness compared to the antivascular endothelial growth factor treatment alone, it does not improve visual acuity and can lead to a higher risk of intraocular pressure elevation. Therefore, these RCTs provide insufficient evidence to determine that the technology results in a meaningful improvement in the net health outcome.

Intravitreal Dexamethasone Implant (0.7 mg) Plus Laser Photocoagulation

Review of Evidence

Randomized Controlled Trials

In 2013, Callanan et al reported a multicenter double masked RCT (N=253) that compared dexamethasone implant plus combination laser photocoagulation to sham treatment plus laser photocoagulation for the treatment of diabetic macular edema.(40) The percentage of patients in the combination group versus the sham group who gained 10 or more letters was greater at 1 month (31.7 vs 11.0, p<.001) and 9 months (31.7% vs 17.3%, p=.007), than at 12 months (27.8% vs 23.6%), respectively. More patients in the sham group discontinued the study due to lack of efficacy (8.7% vs 0.8%), which may have biased results. An increase in IOP of at least 10 mm Hg was observed in 15.2% of eyes treated with dexamethasone implants. In addition, cataract-related adverse events were more common after treatment with dexamethasone implants (22.2% vs 9.5%, p=.017).

Section Summary: Intravitreal Dexamethasone Implant (0.7 g) Plus Laser Photocoagulation for Diabetic Macular Edema

One RCT with 1-year follow-up comparing combination implants plus laser photocoagulation to laser photocoagulation alone found better visual acuity (as measured by gain of ≥10 letters) at 9 months but not at 12 months. But a differential lost to follow-up, lack of power calculations for sample size estimation, and lack of intention-to-treat analysis limit interpretation of results. Use of dexamethasone implants resulted in higher incidences of cataracts and elevated IOP.

AGE-RELATED MACULAR DEGENERATION

Intravitreal Dexamethasone Implant (0.7 mg) Plus Antivascular Endothelial Growth Factor Therapy

Review of Evidence

Randomized Controlled Trials

Kuppermann et al (2015) reported the results of industry-sponsored, single-masked, sham-controlled, randomized trial in which 243 patients with choroidal neovascularization secondary to age-related macular degeneration (AMD) were allocated to dexamethasone implants (n=123) or a sham procedure (n=120).(41) All patients received two protocol-mandated intravitreal ranibizumab injections with the next injection given as needed based on established study criteria. The primary efficacy end point was the ranibizumab injection-free interval at six months. The median injection-free survival was 34 days in the implant group and 29 days in the sham control group. Though this difference was statistically significant (p=.016), the effect size was small and clinically insignificant. The proportions of patients who did not require rescue ranibizumab over the 6-month study period were 8.3% the implant group and 2.5% in the sham group (p=.048). There were no significant differences between the groups in mean change from baseline BCVA. More patients in the dexamethasone implant group had increased IOP (13.2% vs 4.2%; p=.014), but there were no differences between the groups in cataract-related events. Notably, the trial had a short follow-up (6 months).

Section Summary: Intravitreal Dexamethasone Implant (0.7 mg) Plus Antivascular Endothelial Growth Factor Therapy for Age-Related Macular Degeneration

One RCT evaluated the impact of adding implants to a standard VEGF inhibitor for patients with AMD. Results of this trial failed to demonstrate clinically meaningful reductions in the ranibizumab injection-free interval. Further, there was an IOP elevation in greater proportion of patients receiving implants without any additional clinical benefit.

OTHER CONDITIONS

Birdshot Retinochoroidopathy

Birdshot retinochoroidopathy, also known as birdshot chorioretinopathy or vitiliginous chorioretinitis, is a chronic, bilateral rare form of posterior uveitis with characteristic hypopigmented lesions. No RCTs were identified for the treatment of this indication for any corticosteroids intravitreal implants. Bajwa et al (2014) published a retrospective case series involving 11 patients (11 eyes) refractory or intolerant to conventional immunomodulatory therapy who received fluocinolone acetonide implants (0.59 mg).(42) Reported outcomes were disease activity markers. The proportion of patients with intraocular inflammation was 55% at baseline, which decreased to 10%, 11%, and 0% at year one, two, and three, respectively. Active vasculitis was noted in 36.3% patients at baseline and 0% at 3-year follow-up. More

than 20% reduction in central retinal thickness was noted in all patients with cystoid macular edema at six months, one year, two years, and three years' post-implant. Another retrospective cohort study (2015) that included 11 eyes with birdshot chorioretinitis reported improved control of inflammation and decreased reliance on adjunctive therapy with fluocinolone acetonide implants (0.59 mg).(43) Authors observed a more robust increase in IOP compared to the observed elevation in patients with other types of posterior uveitis and panuveitis. Results of another retrospective study by Rush et al (2011), which included 32 eyes with birdshot chorioretinopathy who received fluocinolone acetonide implant (0.59 mg) with 12-month follow-up, also reported decrease in vitreous haze from 26% at baseline to 100% at 12 months.(44) In two small retrospective studies with six eyes in three patients (45) and six eyes in four patients,(46) respectively, reported the favorable effects of dexamethasone implants on ocular inflammation and macular edema during treatment. All eyes exhibited control of ocular inflammation and macular edema. In the first study, all three patients achieved BCVA of at least 20/25 during treatment. In the second, there was a mean improvement of 70 letters on BCVA using the EDTRS chart.

Section Summary: Birdshot Retinochoroidopathy
No RCTs were identified on the treatment of birdshot retinochoroidopathy with any corticosteroids intravitreal implants. Available evidence includes multiple observational studies that noted improvements in anatomic and visual acuity outcomes in individuals refractory or intolerant to current standard of treatment. Long-term follow-up for efficacy and safety is limited. RCTs are needed to permit conclusions on the efficacy of corticosteroid implants in refractory or intolerant patients with birdshot retinochoroidopathy.

Cystoid Macular Edema

Review of Evidence

Randomized Controlled Trials
No large, multi-center, sham-controlled RCTs were identified on the treatment of this indication for any corticosteroids intravitreal implants.

The only RCT identified for this indication is for individuals who have cystoid macular edema related to retinitis pigmentosa. Park et al (2019) published a small (N=14), single-center, observation-controlled RCT from South Korea. (47) In this RCT, (47), 14 patients with bilateral cystoid macular edema related to retinitis pigmentosa with macular cystic changes as shown by spectral domain optical coherence tomography with central macular thickness of .250 mm in both eyes had 1 eye randomized to intravitreal dexamethasone implant 0.7 mg and the other eye was observed. At 2 months, compared to the control eyes, the intravitreal dexamethasone implant eyes resulted in improved central macular thickness(-147.5 μm vs. -14 μm, P<0.001) and median change of best-corrected visual acuity (+6 vs. +1; P<0.001). But, at month6, the central macular thickness of the study eyes returned to baseline level and there were no longer any significant differences between the eyes. At month 12, 40% of study eyes and 12.5%

control eyes experienced cataract formation or progression. But, none required cataract surgery.

Comparative Observational Studies
Three observational studies have compared intravitreal dexamethasone to other treatments in patients with cystoid macular edema. (74,75,48) These studies are heterogenous in the type of cystoid macular edema treated, the comparator treatment, and outcome assessment approaches. The strength and relevancy of their findings is limited as they have included only small numbers of patients and lack responder analysis of the proportion of patients with a 15-or-more letter improvement from baseline in best-corrected visual acuity.

Noncomparative Observational Studies
Multiple case series have assessed improvements in visual acuity and anatomic changes following intravitreal dexamethasone implant (0.7 mg) in patients with cystoid macular edema of various etiologies. (76,77,78,79,80) However, these studies have generally included only small numbers of patients (n range of 26 to 112) and lacked responder analysis of clinically meaningful changes in outcomes. One exception is the case series by Fortoul et al (2015), that evaluated the efficacy of the first intravitreal injection of dexamethasone implant in 26 eyes with cystoid macular edema secondary to retinal vein occlusion over 6 months in a single center in France. (79) Fortoul et al (2015) reported that although 88% of patients achieved at least a 3-line improvement in best-corrected visual acuity 2 months, this was not sustained and only 27.8% of eyes still achieved clinically significant response at 6 months.

Section Summary: Cystoid Macular Edema
Evidence for this indication includes 1 observation-controlled RCT (n=14), 3 comparative observational studies and numerous case series. The RCT found improved mean visual acuity and eye anatomy outcomes with intravitreal dexamethasone compared to the control eyes, but these differences were not sustained at 6 months. The comparative observational studies included 269 patients (range, 60 to 135) and also lacked responder analysis of the proportion of patients with a 15-or-more letter improvement. One case series evaluated the proportion of patients with a 3-lineimprovement in best-corrected visual acuity. Although 88% of patients achieved this outcome at 2 months, the proportion with improvement was not sustained at 6 months (27.8%). Additional blinded, multicenter RCTs are needed that compare intravitreal dexamethasone to another established treatment. The trials should be adequately powered for measuring proportion of patients in whom vision had improved by 15 letters or more.

Idiopathic Macular Telangiectasia Type I

Review of Evidence

Case Reports

No RCTs were identified on the treatment of macular telangiectasia with any corticosteroids intravitreal implants. Three case reports with a total nine patients with type I idiopathic macular telangiectasia treated with dexamethasone implants have described mixed results on improvements in visual acuity and reduction in inflammation.(46,54,55)

Section Summary: Idiopathic Macular Telangiectasia Type I
No RCTs were identified on the treatment of idiopathic macular telangiectasia type I with any corticosteroid intravitreal implants. Available evidence includes multiple case reports, which

have noted mix results for visual acuity and inflammation-related outcomes. Long-term follow-up on efficacy and safety is limited. Better quality studies with long-term follow-up are needed to permit conclusions on the efficacy of corticosteroid implants in patients with this indication.

Postoperative Chronic Macular Edema

Postoperative chronic macular edema, also called as pseudophakic cystoid macular edema or Irvine-Gass syndrome, is one of the most common causes of visual loss after cataract surgery. It is thought to occur as a consequence of inflammatory mediators that are upregulated in the aqueous and vitreous humors after surgical manipulation; it can lead to permanent visual loss.

Review of Evidence

Randomized Controlled Trials

Mylonas et al (2017) published an RCT that compared dexamethasone intravitreal implant to triamcinolone intravitreal injection in 29 patients with refractory postoperative cystoid macular edema. (82) Participants were mostly female (72%) and the mean age was 73 years in the dexamethasone group and 71 years in the triamcinolone group. No primary outcome was specified. There were no significant differences between the groups in improvement in mean best corrected visual acuity, but central millimeter retinal thickness reduction was significantly greater for triamcinolone at 1 week and 6 months. Minimal information on adverse events was reported.

Case Series

Multiple case series have assessed improvements in visual acuity and anatomic changes.(56-62) However, these studies have included only small numbers of patients and reported mean pre-post changes in visual acuity and eye anatomy that lack responder analysis using clinically meaningful changes in outcomes. EPISODIC, a 2016 observational retrospective study conducted in France, included 100 patients with postsurgical macular edema who received dexamethasone implants between April 2011 and June 2014 and who had a minimum of one-year follow-up.(63) Mean improvement in BCVA was 9.6 EDTRS letters at month 6 and 10.3 at month 12. The proportion of eyes with gains in BCVA of 15 or more letters was 32.5% and 37.5% at months 6 and 12, respectively. Average reduction in central subfield macular thickness was 135.2 and 160.9 µm at months 6 and 12.

Section Summary: Postoperative Chronic Macular Edema

Evidence for this indication includes 1 RCT (n=29) that compared dexamethasone intravitreal implant, 0.7 mg to triamcinolone intravitreal injection 4 mg, 2 comparative observational studies and numerous case series. The RCT found no statistically significant difference between treatments in mean visual acuity improvement at 3 or 6 months. The proportion of patients in whom vision had improved by 15 letters or more was not reported. The comparative observational studies included only small numbers of patients and also lack responder analysis of the proportion of patients with a 15-or-more letter improvement. In the largest case series (n=100), 2 of every 5 patients experienced clinically meaningful improvements in visual acuity after 1 year of follow-up. Additional RCTs are needed that have clearly defined and representative populations (ie, for chronic and refractory patients, documentation of intensity and duration of the first-line therapy regimens) and are adequately powered for measuring proportion of patients in whom vision had improved by 15 letters or more.

Circumscribed Choroidal Hemangioma

Case Reports
No RCTs were identified on the treatment of circumscribed choroidal hemangiomas with any corticosteroids intravitreal implants. A single case report has described the use of photodynamic therapy combined with dexamethasone implants. Authors concluded that implants potentiated the effect of photodynamic therapy with less risk of local side effects than triamcinolone acetonide.(64)

Section Summary: Circumscribed Choroidal Hemangiomas
No RCTs were identified on the treatment of circumscribed choroidal hemangiomas with any corticosteroids intravitreal implants. Available evidence includes a single case report that does not permit conclusion on the efficacy and safety of adding dexamethasone implants to photodynamic therapy for treatment of circumscribed choroidal hemangiomas. RCTs are needed to permit conclusions on the efficacy of corticosteroid implants in patients with this indication.

Proliferative Vitreoretinopathy
Proliferative vitreoretinopathy develops as a complication of rhegmatogenous retinal detachment. Proliferative vitreoretinopathy occurs in 8% to 10% of patients undergoing primary retinal detachment surgery and prevents the successful surgical repair of rhegmatogenous retinal detachment. No RCTs were identified on the treatment of proliferative vitreoretinopathy with any corticosteroids intravitreal implants. A case series (2017) of five patients with proliferative vitreoretinopathy has described combined use of surgery, endolaser, and dexamethasone implants.(65) A case report (2013) found a benefit of dexamethasone implants in preventing proliferative vitreoretinopathy in a patient with a rhegmatogenous retinal detachment, who experienced improvements in visual acuity and retinal attachment nine months post-surgery.(66)

Section Summary: Proliferative Vitreoretinopathy
No RCTs were identified on the treatment of proliferative vitreoretinopathy with any corticosteroids intravitreal implants. Available evidence includes one case series and one case report. These studies reported multiple interventions, including dexamethasone implants in conjunction with surgery and laser, for preventing proliferative retinopathy after retinal detachment surgery. RCTs are needed to permit conclusions on the efficacy of corticosteroid implants in patients with proliferative retinopathy.

Radiation Retinopathy
No RCTs were identified on the treatment of radiation retinopathy with any corticosteroids intravitreal implants. In a retrospective study (2015), 12 eyes diagnosed with radiation maculopathy secondary to plaque brachytherapy were treated with dexamethasone implants.(67) Anatomic improvements in foveal thickness were reported, with nonsignificant improvements in visual acuity. In a 2014 retrospective case series, two patients who developed radiation maculopathy after radiotherapy for uveal melanoma were treated with dexamethasone implants.(68) They had limited responses to bevacizumab and intravitreal triamcinolone. Dexamethasone implants provided a prolonged period of anatomic stabilization. In a retrospective chart review of five patients with choroidal melanoma treated with dexamethasone implants for radiation macular edema, Bailif et al (2013) reported mixed improvements in visual acuity.(69) The mean improvement in EDTRS letters was five. Visual acuity improved for three patients (+4, +9, and +15 letters) and remained unchanged for two.

Section Summary: Radiation Retinopathy
No RCTs were identified on the treatment of radiation retinopathy with any corticosteroids intravitreal implants. Available evidence includes multiple observational studies that noted improvements in anatomic stability and visual acuity. RCTs are needed to permit conclusions on the efficacy of corticosteroid implants in patients with radiation retinopathy.

Ocular Inflammation and Pain Following Ophthalmic Surgery

Clinical Context and Test Purpose
The purpose of punctum dexamethasone insert (0.4 mg) is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as standard therapy, in individuals with ocular inflammation and pain following ophthalmic surgery.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with ocular inflammation and pain following ophthalmic surgery.

Interventions
The intervention of interest is the corticosteroid intracanalicular insert, dexamethasone implant (0.4 mg), which is placed in the punctum by a physician during ophthalmic surgery.

Comparators
The comparator of interest is standard of care.

Outcomes
The beneficial outcomes of interest are symptom improvement, change in disease status, functional status and quality of life. Harmful outcomes of interest are treatment-related morbidity. Follow-up over the first few weeks following surgery is of interest for relevant outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
1. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
2. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
3. To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
4. Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Randomized Controlled Trials
For individuals scheduled to undergo clear corneal cataract surgery who receive punctum dexamethasone insert (0.4 mg), the best evidence includes three double-blind, sham-controlled trials of 926 patients (n range, 241 to 438) (Table 12).(70,71) The two initial phase III pivotal trials upon which the FDA approval was based were reported together in 1 publication

by Walters et al (2016)(71). The subsequent larger phase 3C trial was reported by Tyson et al (2019).(70) Coprimary endpoints were identical across all three trials and included evaluating the absence of anterior chamber cells at day 14 and absence of pain at day eight. Compared with the sham insert, all three trials generally consistently found significant improvements with the punctum dexamethasone insert (0.4 mg) across both coprimary efficacy endpoints, as well as for absence of ocular pain at 14 days, with 2 exceptions (Table 11). In the second pivotal trial, the difference between the punctum dexamethasone insert (0.4 mg) and sham did not reach statistical significance for the proportion of patients with an absence of anterior chamber cells at day 14 (absolute difference was 8.1% compared with 18.5% to 21.5%). The other exception was that, absence of pain at day 14 was not reported as a secondary outcome in the large phase 3C trial by Tyson et al (2019). Although that secondary outcome was not prespecified in the protocol, as anterior chamber cells were assessed at day 14, it seems reasonable that pain could have been assessed at that time as well. This raises a question about potential reporting bias. Adverse events were generally similar between punctum dexamethasone insert (0.4 mg) and sham. The most common types of adverse events were anterior chamber inflammation, iritis, and increased intraocular pressure. Although allocation concealment methods are unclear across the studies, they had no major methodological limitations (Tables 12 and 13). Based on the consistent benefits and lack of important increases in adverse event risk, evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Table 12. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	*Comparator*
Walters et al (2016); Study 1 (OTX-13-002; NCT02034019)	U.S.	16	Not reported	≥ 18 yrs of age, with a visually significant cataract and scheduled to undergo clear corneal cataract surgery with phacoemulsification and implantation of a posterior chamber intraocular lens	Punctum dexamethasone insert (0.4 mg), N=164	Sham, N=83
Walters et al (2016); Study 2 (OTX-13-003; NCT02089113)	U.S.	16	Not reported	Same as Walters et al 2016 study 1	Punctum dexamethasone insert (0.4 mg), N=161	Sham, N=80
Tyson et al (2019) (NCT02736175)	U.S.	21	Not reported	≥ 18 yrs of age, presence of a cataract and plans to undergo clear corneal cataract surgery with phacoemulsification and implantation of a posterior chamber a posterior chamber intraocular lens	Punctum dexamethasone insert (0.4 mg, N=216	Sham, N=222

NCT02736175: A Prospective, Multicenter, Randomized, Parallel-Arm, Double-Masked, Vehicle Controlled Phase 3C Study Evaluating the Safety and Efficacy of OTX-DP for the Treatment of Ocular Inflammation and Pain After Cataract Surgery; OTX-13-002 : Phase 3 Study Evaluating Safety and Efficacy of OTX-DP for Treatment of Ocular Inflammation and Pain After Cataract Surgery; OTX-13-003 : A Prospective, Multicenter, Randomized, Parallel-Arm, Double-Masked, Vehicle Controlled Phase 3B Study Evaluating the Safety and Efficacy of OTX-DP for the Treatment of Ocular Inflammation and Pain After Cataract Surgery; RCT: randomized controlled trial.

Table 13. Summary of Key RCT Results

Study	Absence of Ocular Pain at Day 8	Absence of Ocular Pain at Day 14	Absence of Anterior Chamber Cells at Day 14	Serious adverse events	Increased intraocular pressure
Walters et al (2016) Study 1	247	247	247	246	246
Punctum dexamethasone insert (0.4 mg)	n NR (80.4%)	n NR (79.6%)	54 (33.1%)	3 (1.9%)	11 (6.8%)
Sham	n NR (43.4%)	n NR (39.8%)	12 (14.5%)	5 (6.0)	3 (3.6%)
P-value	<0.0001	<0.0001	0.0018		NR
Walters et al (2016); Study 2	241	241	241	240	240
Punctum dexamethasone insert (0.4 mg)	n NR (77.5%)	n NR (76.9%)	63 (39.4%)	2 (1.2%)	7 (4.4%)
Sham	n NR (58.8%)	n NR (57.5%)	25 (31.3%)	3 (3.8%)	4 (5.0%)
P-value				NR	NR
	=0.0025	=0.0019	=0.2182		
Tyson et al (2019)	438	NA	438	437	437
Punctum dexamethasone insert (0.4 mg)	n NR (79.6%)	NR	n NR (52.3%)	3 (1.4%)	16 (7.4%)
Sham	n NR (61.3%)	NR	n NR (31.1%)	2 (0.9%)	6 (2.7%)
P-value	<0.0001	NR	<0.0001	NR	NR

NR=not reported; (OTX-13-002): Phase 3 Study Evaluating Safety and Efficacy of OTX-DP for Treatment of Ocular Inflammation and Pain After Cataract Surgery; (OTX-13-003): A Prospective, Multicenter, Randomized, Parallel-Arm, Double-Masked, Vehicle Controlled Phase 3B Study Evaluating the Safety and Efficacy of OTX-DP for the Treatment of Ocular Inflammation and Pain After Cataract Surgery; RCT: randomized controlled trial.

Table 14. Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Walters et al (2016) Study 1					
Walters et al (2016) Study 2					
Tyson et al (2019)	1. 14-day absence of pain not reported				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

a Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.

b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.

c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 15. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Walters et al (2016) Study 1	3. Allocation concealment unclear					

Walters et al (2016) Study 2	3. Allocation concealment unclear		
Tyson et al (2019)	3. Allocation concealment unclear	4. Described as double-blind, but outcome assessor unspecified	2. Although 14-day pain was not listed as a planned outcome in the CT.gov protocol, it could have reasonably been assessed at day 14 along with chamber cells

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician; 4. Unclear blinding of outcome assessment

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Ocular Inflammation and Pain Following Ophthalmic Surgery

For individuals scheduled to undergo clear corneal cataract surgery who receive punctum dexamethasone insert (0.4 mg), the evidence includes three RCTs. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment related morbidity. Compared with the sham insert, all three trials generally consistently found significant improvements with the punctum dexamethasone insert (0.4 mg) across both coprimary efficacy endpoints of absence of pain at eight days and absence of anterior chamber cells at day 14. Adverse events were generally similar between punctum dexamethasone insert (0.4 mg) and sham. Based on the consistent benefits and lack of important increases in adverse event risk, evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Dextenza and Allergic Conjunctivits

Torkildsen et al. (2017) report on the results of a phase 2, randomized, double-masked, vehicle-controlled clinical trial evaluating the efficacy and safety of Detenza in a model of allergic conjunctivitis. (97) Fifty-nine subjects (n=28 Dextenza group, n=31 vehicle group) with a positive conjunctival allergen challenge (CAC) were randomized to receive Dextenza or PV (vehicle insert). Challenges occurred over 42 days, with efficacy assessed at 14 (primary endpoint visit), 28, and 40 days postinsertion. Outcome measures included the evaluation of ocular itching, redness, tearing, chemosis, eyelid swelling, rhinorrhea, and congestion. At 14 days postinsertion, Dextenza was statistically superior to PV, with least square mean differences for ocular itching of -0.76, -0.97, and -0.87 at 3, 5, and 7 min post-CAC, and for conjunctival redness of -0.46, -0.66, and -0.68 at 7, 15, and 20 min post-CAC. Clinical significance, defined as a 1-U decrease from PV, was not met for primary efficacy. Secondary endpoints, including number of subjects reporting itching and conjunctival redness, indicated superior performance of Dextenza compared with vehicle. Eleven Dextenza-treated (35.5%) and 10 vehicle-treated (30.3%) subjects each experienced a single adverse event. The authors

state that this phase 2 study demonstrated preliminary efficacy and safety data of Dextenza for the treatment of allergic conjunctivitis.

On October 11, 2021, the United States Drug and Food Administration (FDA) granted approval of Supplemental New Drug Application (sNDA) to expand the use of Dextenza (dexamethasone ophthalmic insert) with an additional indication for the treatment of ocular itching associated with allergic conjunctivitis. This FDA approval was based on efficacy data from three randomized multicenter, double-masked, parallel group, vehicle-controlled studies utilizing a repeat conjunctival allergen challenge model in participants (n=255) with a positive history of ocular allergies and positive skin test reaction to perennial and seasonal allergens. In all three studies, the Dextenza group demonstrated lower mean ocular itching scores in comparison to the vehicle group at all time points throughout the 1-month course of the study. Additionally, two of the three studies demonstrated a higher proportion of participants having statistically significant reductions in ocular itching on day 8, at 3 minutes, 5 minutes and 7 minutes post-challenge in the Dextenza group in comparison to the vehicle group (Ocular Therapeutix, 2021a; 2021b). (98,99)

Prophylaxis of Cystoid Macular Edema in Individuals with Noninfectious Intermediate Uveitis or Posterior Uveitis and Cataract Undergoing Cataract Surgery

Clinical Context and Test Purpose
The purpose of intravitreal dexamethasone implant 0.7 mg as prophylaxis of cystoid macular edema in individuals with noninfectious intermediate uveitis or posterior uveitis and cataract undergoing cataract surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as systematic corticosteroids.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with noninfectious intermediate uveitis or posterior uveitis and cataract undergoing cataract surgery.

Interventions
The intervention of interest is prophylactic intravitreal dexamethasone implant 0.7 mg.

Comparators
The comparator of interest is standard of care.

Outcomes
The beneficial outcomes of interest are symptom improvement, change in disease status, functional status and quality of life. Harmful outcomes of interest are treatment-related morbidity.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

1. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
2. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
3. To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
4. Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Randomized Controlled Trials

For individuals with noninfectious intermediate uveitis or posterior uveitis and cataract undergoing cataract surgery who receive of intravitreal dexamethasone implant 0.7 mg, the best evidence includes one single-center, open-label RCT of 43 patients in India (Table 14).(72) Compared with prophylaxis with systemic corticosteroids, intravitreal dexamethasone 0.7 mg led to similar rates of cystoid macular edema and change in best-corrected visual acuity and avoided need for early steroid taper due to adverse effects on blood glucose, but potentially increased risk of developing intraocular pressure (Table 15). These findings should be interpreted with caution, however, to due important study limitations including its small sample size, unclear allocation concealment methods and lack of blinding (Tables 16 and 17). Due to these important limitations, evidence is insufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Table 16. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	*Comparator*
Sudhalkar et al (2019)	India	1	2015-2016	≥ 18 yrs of age, previous unilateral recurrent noninfectious intermediate uveitis or posterior uveitis with CMO and cataract of sufficient degree to warrant surgery; well-controlled uveitis for at least 3 mos. prior to scheduled date of cataract surgery	Intravitreal dexamethasone 0.7 mg, N=20	Oral corticosteroids, N=23

CMO: cystoid macular edema; RCT: randomized controlled trial.

Table 17. Summary of Key RCT Results

Study	Development of CMO at 6 mos	BCVA at 6 mos	Developed ocular hypertension	Required rapid taper of systemic steroids due to adverse blood glucose effects
Sudhalkar et al (2019)	43	43	43	43
Intravitreal dexamethasone 0.7 mg	1 (5%)	0.04 logMAR	4 (20%)	0
Oral corticosteroids	2 (8%)	0.06 logMAR	0	3 (13%)
P-value	NR, but described as NSD	0.42	NR	NR

BCVA: best-corrected visual acuity; CMO: cystoid macular edema; logMAR: logarithm of the minimal angle of resolution; NR: not reported; NSD: not significantly different; RCT: randomized controlled trial.

Table 18. Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Sudhalkar et al (2018)	4. Study population potentially had better prognosis than intended use				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

a Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 19. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Sudhalkar et al (2018)	3. Allocation concealment unclear	1. Not blinded				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician; 4. Unclear blinding of outcome assessment
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

SUMMARY OF EVIDENCE

Uveitis

For individuals with chronic noninfectious intermediate or posterior uveitis who receive an intravitreal fluocinolone acetonide implant (0.59 mg), the evidence includes 4 randomized controlled trials (RCTs). Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Two of the four RCTs compared two doses of implants and two trials compared implants with systemic steroids (and immunosuppression when indicated). All trials supported the efficacy of intravitreal fluocinolone acetonide implants in preventing recurrence and improving visual acuity over four-year follow-up. The head-to-head trial comparing implants with systemic corticosteroids did not show substantial superiority in the overall effectiveness of either approach. After 24 and 54 months of follow-up, visual acuity improved from baseline in the implant groups compared to the systematic therapy groups by +6.0 and +3.2 letters (p=.16) and +2.4 and 3.1 letters (p=.073),

respectively. However, nearly all phakic patients receiving implants developed cataracts and required cataract surgery. Further, most also developed glaucoma, with 75% of patients requiring intraocular pressure (IOP)-lowering medications and 35% requiring filtering surgeries. Systemic adverse events such as hyperlipidemia, diabetes, osteoporosis, fractures, and blood count/chemistry abnormalities were infrequent and not statistically distinguishable between groups. The incidence of hypertension was greater in the systemic therapy group (27%) compared to the implant group (13%), but rates of antihypertensive treatment initiation did not differ. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with noninfectious intermediate or posterior uveitis who receive an intravitreal dexamethasone implant (0.7 mg), the evidence includes one RCT. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Results of this trial at 8 weeks showed that the implant was effective in reducing inflammation (the proportion of eyes with no inflammation was 47% and 12% with implant and sham, respectively) and resulted in clinically meaningful improvement in vision at week eight compared to sham controls (the proportion of patients with a gain of ≥15 letters in best-corrected visual acuity [BCVA] from baseline was ~40% with implants and 10% with sham). Further, at week 26, patients treated with implants reported meaningful increases in vision-related functioning. The major limitation of this trial was its lack of long-term follow-up. Use of implants resulted in higher incidences of cataracts and elevated IOP. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Macular Edema

For individuals with macular edema after retinal vein occlusion who receive an intravitreal dexamethasone implant (0.7 mg), the evidence includes 2 RCTs. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Compared to sham controls, implants resulted in clinically meaningful improvements in visual acuity within one to three months post-implant and improvement in vision occurred faster. The difference in the proportion of patients with gain of 15 or more letters in BCVA from baseline was more than 10% in favor implants versus sham in both studies at 30, 60 and 90 days, but not at 180 days post-implant. Use of implants resulted in higher incidences of cataracts and elevated IOP. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with macular edema after retinal vein occlusion who receive an intravitreal fluocinolone acetonide implant (0.59 mg), no relevant studies were identified. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. The evidence is insufficient to determine the effects of the technology on health outcomes.

Diabetic Macular Edema

For individuals with refractory (persistent or recurrent) diabetic macular edema (DME) who receive an intravitreal fluocinolone acetonide implant (0.59 mg), the evidence includes an RCT. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Compared to standard of care (as needed laser or observation), a greater proportion of patients with implants reported clinically significant improvement in vision at six months (1.4% vs 16.8% respectively) and subsequent time points assessed but not at or beyond 30 months of follow-up. Ninety percent of patients with phakic eyes who received implants required cataract surgery and 60% developed elevated IOP. Due

to the substantial increase in adverse events and availability of agents with safer tolerability profiles (eg, anti-vascular endothelial growth factor [anti-VEGF]), implant use in DME is questionable. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with diabetic macular edema who receive an intravitreal fluocinolone acetonide implant (0.19 mg), the evidence includes two RCTs. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Implant-treated eyes showed in clinically meaningful improvements in vision at two and three years' post-implant. The percentage of patients who gained 15 letters or more was 28.7% in the implant group versus 18.9% in the sham group at three years. Subgroup analysis showed greater improvements in visual acuity in patients who were pseudophakic compared to those who were phakic (difference in mean change in number of letters at two years from baseline was 5.6 letters in pseudophakic patients vs one letter in phakic patients). A major limitation of these implants is that nearly 80% all phakic patients will develop cataracts and will require cataract surgery. Further, IOP was elevated in 34% of patients who received this implant compared with 10% of controls. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with diabetic macular edema who receive an intravitreal dexamethasone implant (0.7 mg), the evidence includes three RCTs. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Compared to sham control, two identically designed RCTs showed clinically meaningful improvements in vision with dexamethasone implants that peaked at three months and maintained 39 months (with retreatment). The difference in proportion of patients with a gain of 15 or more letters in BCVA from baseline was 9.3% and 13.0% in the two trials, respectively, favoring implant versus sham at 39 months post-implant. Subgroup analysis of these trials showed greater improvements in visual acuity in patients who were pseudophakic compared to those who were phakic. Results of 1 small RCT showed that, compared to bevacizumab, implant-treated patients at one year had similar improvement rates on the primary end point, but experienced greater rates of vision loss (0% vs 10.9%), greater frequency of side effects such as cataracts (4.8% vs 13%), and elevated IOP (0% vs 19.6%), all respectively. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with diabetic macular edema who receive an intravitreal dexamethasone implant (0.7 mg) plus anti-VEGF therapy, the evidence includes two RCT. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Findings from both RCTs were consistent in demonstrating that although adding dexamethasone to an antivascular endothelial growth factor treatment can lead to a greater mean reduction in central subfield thickness, it does not improve visual acuity and can lead to a higher risk of intraocular pressure elevation. Based on the consistent lack of improvement in visual acuity, increased risk of intraocular pressure elevation, and imprecision, these RCTs provide insufficient evidence to determine that the technology results in an improvement in the net health outcome.

For individuals with diabetic macular edema who receive an intravitreal dexamethasone implant (0.7 mg) plus laser photocoagulation, the evidence includes an RCT. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. One RCT with one-year follow-up demonstrated that combination

implants plus laser photocoagulation compared to laser photocoagulation alone resulted in better visual acuity (as measured by gain of ≥10 letters) at 9 months but not at 12 months. However, the generally acceptable standard outcome measure for change is 15 or more letters and it was not used in this trial. The use of dexamethasone implants resulted in higher incidences of cataracts and elevated IOP Further, a differential loss to follow-up, lack of power calculations for sample size estimation, and lack of intention-to-treat analysis preclude interpretation of results. A larger RCT with adequate power is needed to confirm these findings. The evidence is insufficient to determine the effects of the technology on health outcomes.

Age-Related Macular Degeneration
For individuals with age-related macular degeneration who receive an intravitreal dexamethasone implant (0.7 mg) plus anti-VEGF inhibitor, the evidence includes 1 RCT. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Results of this trial did not demonstrate clinically meaningful reductions in the ranibizumab injection-free interval between combined treatments (34 days) and anti-VEGF alone (29 days; p=0.016). Further, IOP was elevated in a greater proportion of patients receiving implants without any additional clinical benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Other Conditions
For individuals with birdshot retinochoroidopathy refractory or intolerant to standard therapy who receive an intravitreal fluocinolone acetonide implant (0.59 mg) or intravitreal dexamethasone implant (0.7 mg), the evidence includes multiple observational studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Multiple observational studies have noted improvements in anatomic and visual acuity outcomes. Long-term follow-up for efficacy and safety is limited. RCTs are needed to permit conclusions on the efficacy of corticosteroid implants in refractory or intolerant patients with birdshot retinchoroidopathy. The evidence is insufficient to determine the effects of that the technology results in an improvement in the net health outcome.

For individuals with cystoid macular edema related to retinitis pigmentosa who receive an intravitreal dexamethasone implant (0.7 mg), the evidence includes multiple case reports. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Case reports have noted mix results for anatomic and visual acuity outcomes. Long-term follow-up for efficacy and safety is limited. Larger RCTs are needed to permit conclusions on the efficacy of corticosteroid implants in patients with cystoid macular edema related to retinitis pigmentosa. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with idiopathic macular telangiectasia type I who receive an intravitreal dexamethasone implant (0.7 mg), the evidence includes multiple case reports. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Case reports have noted mix results for visual acuity and inflammation-related outcomes. Long-term follow-up for efficacy and safety is limited. Better quality studies with long-term follow-up are needed to permit conclusions on the efficacy of corticosteroid implants in patients with idiopathic macular telangiectasia type I. The evidence is insufficient to determine the effects of the technology on health outcome.

For individuals with postoperative chronic macular edema who receive an intravitreal dexamethasone implant (0.7 mg), the evidence includes multiple observational studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Of multiple observational studies, one large retrospective analysis of 100 patients showed that two of every five patients experienced clinically meaningful improvements in vision at one-year follow-up. An RCT is needed to confirm the efficacy of corticosteroid implants in patients with postoperative chronic macular edema. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with circumscribed choroidal hemangiomas who receive an intravitreal dexamethasone implant (0.7 mg) plus photodynamic therapy, the evidence includes a one case report. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Results of the case report do not permit conclusions about the efficacy and safety of adding dexamethasone implants for circumscribed choroidal hemangiomas to photodynamic therapy. RCTs are needed to permit conclusions on the efficacy of corticosteroid implants in patients with circumscribed choroidal hemangiomas. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with proliferative vitreoretinopathy who receive an intravitreal dexamethasone implant (0.7 mg), the evidence includes 1 case series and 1 case report. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. These studies have reported multiple interventions, including dexamethasone implants in conjunction with surgery and laser for preventing proliferative retinopathy after retinal detachment surgery. RCTs are needed to permit conclusions on the efficacy of corticosteroid implants in patients with proliferative retinopathy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with radiation retinopathy who receive an intravitreal dexamethasone implant (0.7 mg), the evidence includes multiple observational studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Multiple observational studies have noted improvements in anatomic and visual acuity outcomes. Long-term follow-up for efficacy and safety is limited. RCTs are needed to permit conclusions on the efficacy of corticosteroid implants in patients with radiation retinopathy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with ocular inflammation and pain following ophthalmic surgery or for individuals with ocular itching associated with allergic conjunctivitis who receive punctum dexamethasone insert (0.4 mg), the evidence includes 4 RCTs. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment related morbidity. All three trials noted significant improvements with the punctum dexamethasone insert (0.4 mg) across both coprimary efficacy endpoints of absence of pain at eight days and absence of anterior chamber cells at day 14. Adverse events were generally similar between punctum dexamethasone insert (0.4 mg) and sham. One phase 2 RCT demonstrated preliminary efficacy and safety data of Dextenza for the treatment of allergic conjunctivitis. Based on the consistent benefits and lack of important increases in adverse event risk, evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with noninfectious intermediate uveitis or posterior uveitis and cataract undergoing cataract surgery who receive prophylaxis with intravitreal dexamethasone implant 0.7 mg, the best evidence includes one single-center, open label RCT of 43 patients in India. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment related morbidity. Compared with oral corticosteroids, intravitreal dexamethasone 0.7 mg had similar benefits and avoided need for early steroid taper due to adverse effects on blood glucose, but potentially increased risk of developing intraocular pressure. Due to important study limitations including its small sample size, unclear allocation concealment methods and lack of blinding, evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

CLINICAL INPUT RECEIVED THROUGH PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, Blue Cross Blue Shield Association received input from one physician specialty society and one academic medical center while this policy was under review in 2011. Input supported use of intravitreal corticosteroid implants, confined to indications labeled by the FDA. It was noted that Ozurdex (intravitreal dexamethasone implant 0.7 mg) is used for short-term uveitis control while the Retisert (intravitreal fluocinolone acetonide implant 0.59 mg) implant is used for more long-term control of uveitis.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Academy of Ophthalmology

In 2019, the American Academy of Ophthalmology published its preferred Practice Pattern® for retinal vein occlusions.(73) The Academy stated: “Macular edema may complicate both central retinal vein occlusions and branch retinal vein occlusions. The first line of treatment for associated macular edema is anti-vascular endothelial growth factors. Intravitreal corticosteroids, with the associated risk of glaucoma and cataract formation, have demonstrated efficacy. Also, laser photocoagulation surgery in branch retinal vein occlusion has a potential role in treatment."

In 2019, the American Academy of Ophthalmology published its preferred Practice Pattern® for diabetic retinopathy. (87) Related to therapy with intravitreal corticosteroids, the Academy stated: "Because of their side-effect profile, including cataract progression and elevated IOP [intraocular pressure], they [intravitreal corticosteroids] are generally used as second-line agents for DME [diabetic macular edema], especially for phakic patients."

In 2019, the American Academy of Ophthalmology published its preferred Practice Pattern® for age-related macular degeneration. (88) Regarding intravitreal corticosteroid use, the Academy stated that the "data do not currently support the use of combination therapy with steroids, especially given the long-term side effects of glaucoma and cataract that are associated with corticosteroid use."

National Institute for Health and Care Excellence

In 2019, National Institute for Health and Care Excellence (NICE) released guidance on the use of fluocinolone acetonide intravitreal implant 0.19 mg (Iluvien) for treating chronic diabetic macular edema that is insufficiently responsive to available therapies in an eye with a natural lens (phakic eye).(89) The NICE guidance states, “Fluocinolone acetonide intravitreal implant is not recommended as an option for treating chronic diabetic macular oedema that is insufficiently responsive to available therapies in an eye with a natural lens (phakic eye).” The NICE committee reached this conclusion based on their interpretation that “results from [Fluocinolone Acetonide in Diabetic Macular Edema] FAME may not be generalisable to people with chronic diabetic macular oedema in phakic eyes with symptomatic cataract seen in the NHS” because “in FAME, very few people had symptomatic cataract at baseline” and that the type of rescue therapy used in FAME is not used in National Health Service (NHS) clinical practice.

In 2019, NICE released guidance on the use of fluocinolone acetonide intravitreal implant for treating recurrent noninfectious uveitis.(90) The guidance stated, "Fluocinolone acetonide intravitreal implant is recommended, within its marketing authorization, as an option for preventing relapse in recurrent non-infectious uveitis affecting the posterior segment of the eye."

In 2017, NICE released guidance on the use of dexamethasone intravitreal implant (with adalimumab) for the treatment of noninfectious uveitis.(91) NICE recommended the implant only in cases of “active disease” with “worsening vision” and the “risk of blindness.”

In 2011, NICE provided guidance on the use of the dexamethasone intravitreal implant for macular edema secondary to retinal vein occlusion.(92) The dexamethasone implant was recommended as an option for the treatment of macular edema following retinal vein occlusion. NICE also recommended it as an option for treating macular edema following branch retinal vein occlusion when treatment with laser photocoagulation has not been beneficial or suitable.

In 2022, NICE provided guidance on the dexamethasone intravitreal implant (Ozurdex) for treating diabetic macular edema.(93) Ozurdex was recommended as a possible treatment for patients with diabetic macular edema “only if their condition has not responded well enough to, or if they cannot have non-corticosteroid therapy." This recommendation is irrespective of whether patients have a phakic or pseudophakic lens.

In 2013, NICE updated its guidance on the intravitreal fluocinolone acetonide implant (Iluvien), recommending as an option for treating patients with chronic diabetic macular edema that is insufficiently responsive to available therapies only if: “the implant is to be used in an eye with an intraocular [pseudophakic] lens and their diabetic macular oedema has not got better with other treatments.”(94)

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 18.

Table 18. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05101928	Ozurdex as Monotherapy for Treatment of Non-infectious Intermediate, Posterior, or Panuveitis	84	Feb 2025
NCT04469595	A Randomized, Masked, Controlled Study of Intravitreal ILUVIEN® Implant as Baseline Therapy in Patients With Early Diabetic Macular Edema (DME)	300	Dec 2024
NCT05003258	Functional and Anatomical Outcomes of Dexamethasone Intra- vitreal Implant in Patients With Resistant Macular Edema Secondary to Retinal Vein Occlusion After Intravitreal Anti-VEGF Injection	25	Oct 2024
Unpublished			
NCT01827722	Ozurdex® Versus Ranibizumab Versus Combination for Central Retinal Vein Occlusion	45	Dec 2016 (unknown)
NCT01998412[a]	An Open Label, Registry Study of the Safety of Iluvien® 190 Micrograms Intravitreal Implant in Applicator	559	Jan 2020 (unknown)
NCT02556424[a]	Efficacy and Tolerance Comparison Between Subconjunctival Injection of Triamcinolone and Intravitreal Implant of Dexamethasone for the Treatment of Inflammatory Macular Edema	114	Feb 2021
NCT02471651[a]	Dexamethasone Intravitreal Implant (0.7mg) for the Treatment of Persistent Diabetic Macular Edema Following Intravitreal Anti-Vascular Endothelial Growth Factor Therapy	40	Oct 2018 (has results, but no peer-reviewed publication)
NCT03003416	Efficacy of Ozurdex® in the Treatment of Diabetic Macular Edema	115	Dec 2018 (completed)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

Government Regulations

National:

There is no national or local coverage determination. CMS has issued fee schedules for codes 67027 and 67028.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Intraocular Lens Implantation for Myopia (Nearsightedness)
- Retinal Prosthesis

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through May 9, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/12	6/12/12	6/15/12	Joint policy established
1/1/13	10/16/12	10/16/12	Added code 67028 to policy
11/1/13	8/22/13	8/27/13	Codes J7310-12 added to policy; policy position unchanged; Rationale and References updated.
3/1/15	12/9/14	12/29/14	Routine maintenance; added "diabetic macular edema" as an indication for Ozurdex®; added Iluvien™ to MPS and inclusion sections; removed J7310.
5/1/16	2/16/16	2/16/16	Routine maintenance; updated references and rationale. Added code J7313.
5/1/17	2/21/17	2/21/17	• Routine maintenance
5/1/18	2/20/18	2/20/18	• Routine maintenance • Updated references and rationale
5/1/19	2/19/19		• Routine maintenance
1/1/20	10/15/19		• Routine maintenance • Yutiq added per FDA recommendation
1/1/21	10/20/20		• Title adjusted to include punctum • Punctum implants incorporated – Dextenza as EST • 0356T and J1096 added as EST (Dextenza) • Clarification added to exclude dexamethasone and fluocinolone acetonide intravitreal implants in cystoid macular edema for individuals with noninfectious intermediate uveitis or posterior uveitis undergoing cataract surgery.
1/1/22	10/19/21		• Routine maintenance, no change in policy. • References 74-82 added
1/1/23	10/18/22		• Routine maintenance, no change in policy. (ky)

1/1/24	10/17/23		• Routine maintenance, no change in policy. Vendor: N/A. (ky)
9/1/24	6/11/24		• Routine maintenance, FDA expanded coverage of Dextenza Oct, 2021 to include treatment of ocular itching associated with allergic conjunctivitis. Vendor: N/A. (ky)

Next Review Date: 2nd Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: INTRAVITREAL AND PUNCTUM CORTICOSTEROID IMPLANTS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered, criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.